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ORIGINAL ARTICLES

EFFECTS OF WITHHOLDING FLUID IN THE IMMEDIATE POSTNATAL PERIOD

By JOHN D. L. HANSEN, M. B. (Capetown), M.R.C.P.,*
AND CLEMENT A. SMITH, M.D.
Boston

INHALATION of food or of gastric contents is a well recognized hazard during the newborn period and a frequent cause of neonatal morbidity and mortality.[1] This applies particularly to premature infants and those whose adjustment to postnatal life is complicated by respiratory difficulty from other causes, cerebral hemorrhage, edema or certain congenital abnormalities. Clinical observation in this hospital has shown that feeding, with its attendant dangers, may be delayed for 48 hours after birth in the great majority of infants. Since premature infants and those with apparent edema born to diabetic mothers appear to tolerate a further extension of this period, omission of feeding or other fluid administration to such infants for 3 to 4 days has been a successful regime for some years in these nurseries.[2-4] The threat of serious pulmonary pathology has thus been minimized at this early and critical phase of postnatal life.

The tolerance of newborn infants to restriction of fluid intake has suggested that their greater body water content[5] may offer a reserve for excretory needs beyond that available later in life. These studies were undertaken primarily to test this hypothesis and to determine whether the provision of water significantly influences removal of electrolytes and nitrogen in the urine and concentrations of these substances in body fluids. The investigations included also a further series of infants given water plus glucose to ascertain whether glucose produces in newborn infants the protein- and sodium-sparing effects demonstrated by Gamble in adults.[6]

From the Boston Lying-in Hospital and the Infants' Hospital, Boston, and the Department of Pediatrics, Harvard Medical School, Boston.

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TABLE 1

DESCRIPTIVE DATA, URINE VOLUMES AND RENAL EXCRETIONS OF ELECTROLYTES AND NITROGEN IN 25 INFANTS STUDIED, DURING FIRST 3 DAYS AFTER BIRTH

Infant	Gestation (wk.)	Length (cm.)	Weight (gm.)	3 Day Weight Loss (per cent)	Average Values/Kg./Day for 3 Days						
					Intake cc.	Water	Urine Vol. (cc.)	Na mEq.	K mEq.	Cl mEq.	N mg.
INFANTS FASTING WITH WATER INTAKE											
T_1*	33	42	1652	9.2	102	Water	97	1.29	1.71	1.33	129
M	32	39	1650	9.1	36	"	42	1.20	1.31	1.25	118
AVE. More Premature Infants				9.2	69	"	70	1.25	1.51	1.29	124
D	36	44	2340	10.5	33	"	26	0.54	0.93	0.60	127
P	36	44	1960	8.9	50	"	34	0.33	0.40	0.47	94
S	36	42	2290	4.8	46	"	24	0.14	0.26	0.11	81
B_1*	38	48	2465	6.3	44	"	29	0.17	0.69	0.45	98
AVE. Less Premature Infants				7.6	43	"	28	0.30	0.57	0.41	100
Ma	40	49	3230	8.2	35	"	21	0.34	0.31	0.38	73
Ga	40	56	4655	7.6	40	"	13	0.23	0.23	0.24	62
Gi	39	49	3360	9.6	38	"	31	0.59	0.77	0.65	95
AVE. Term Infants				8.5	38	"	22	0.39	0.44	0.42	77
INFANTS FASTING WITHOUT WATER INTAKE											
T_2*	33	42	1583	13.3	0	0	24	1.13	1.48	1.43	127
N	34	42	2175	16.1	0	0	26	1.53	1.23	0.98	151
L	30	38	1165	17.8	0	0	21	1.21	1.83	0.93	126
AVE. More Premature Infants				15.7	0	0	23	1.29	1.51	1.11	135
Me	38	47	2432	12.4	0	0	8	0.39	0.30	0.29	59
C	37	47	2365	9.7	0	0	9	0.11	0.32	0.07	64
B_2*	38	48	2450	11.0	0	0	10	0.19	0.53	0.41	63
AVE. Less Premature Infants				11.0	0	0	9	0.23	0.38	0.26	62
Sh	40	53	3620	14.1	0	0	15	0.23	0.39	0.27	68
W	40	51	3510	14.4	0	0	12	0.50	0.80	0.60	96
Gr	40	53	3544	14.2	0	0	10	0.32	0.56	0.55	73
AVE. Term Infants				14.2	0	0	12	0.35	0.58	0.47	79
					Intake cc.	Glucose					
INFANTS RECEIVING GLUCOSE AND WATER											
Fi	33	41	1620	4.3	49	5%	31	0.44	0.90	0.25	120
Pa	32	42	1510	8.3	57	10%	31	1.19	0.74	0.41	171
AVE. More Premature Infants				6.3	53		31	0.82	0.82	0.33	146
Wi	37	46	2430	7.4	42	10%	19	0.40	0.47	0.31	81
Hi	38	47	2400	5.6	49	10%	23	0.21	0.84	0.28	109
Dun	40	47	2870	4.3	38	2.5%	16	0.10	0.15	0.15	67
Bl	41	53	4120	7.2	50	2.5%	38	0.59	0.61	1.22	76
Ja	40	50	4010	4.7	40	10%	26	0.24	0.44	0.76	94
AVE. Less Premature and Term Infants				5.8	44		24	0.31	0.50	0.54	85

* Twins.

Methods

Complete 24 hr. collections of urine were made daily following birth, as previously described from this laboratory,[3] and analyzed for Na and K with the flame photometer,[7] for N by macro-Kjeldahl,[8] for Cl by the method of Van Slyke and Hiller[9] and for urine osmolarity by calculation from depression of freezing point.[10] Stools were collected separately for weighing but were not analyzed as they consisted mainly of meconium. Venous or capillary blood samples were taken at birth, at 72 hr. and 96 hr. Serum was analyzed for Na and K by flame photometry, using 0.2 cc. samples,[7] for Cl by micro method of Van Slyke and Hiller using 0.04 cc. samples[9] and for B.U.N. by the urease method.[11]

All infants were weighed daily on an accurate balance. Water and feedings were given by nipple or gavage, the containers being weighed before and after feedings.

Effects of Withholding Water

These effects were observed over the first three days following birth, on a basis of fasting. Measurements obtained from nine infants receiving a moderate water intake were compared with those from another group of nine fasting infants who were not given

TABLE 2

Serum Concentrations at Birth, 72 Hours and 96 Hours

Infant	Na mEq./l.			Cl mEq./l.			K mEq./l.			B.U.N. mg./100 cc.		
	Birth	72 hr.	96 hr.	Birth	72 hr.	96 hr.	Birth	72 hr.	96 hr.	Birth	72 hr.	96 hr.
INFANTS FASTING WITH WATER INTAKE												
T_1*	150	131	141	102	109	110	5.3	5	5	6	12	5.5
M	145	148	—	107	98	93	6.5	5	6	17.6	21	16.5
D	141.5	138.7	147	104.3	100.3	103	7.5	3	3.9	31.6	22.4	14.2
P	140	136	137	104	103	96	6	5.6	3	24	19	15
S	142	135	130	106	97	90	5.6	5.1	4.9	15.8	12.2	9.2
B_1*	143	139	142	105	103	106	5.6	4.5	3.7	18	11	10
Ma	138	138	138	100	95	96	3.8	4	4.2	28	20	19
Ga	136	138	132	108	98	96	6.4	3	3.4	21	23	19
Gi	138	135	140	104	104	101	5.7	5.3	5.3	21	24	18
INFANTS FASTING WITHOUT WATER INTAKE												
T_2*	136	147	142	105	108	105	6	4	5.7	7	17	12
N	136	150	145	100	111	105	4.7	5.6	3.6	15	29	19
Me	145	162	138	112	116	106	4.6	5.9	5.9	16	17	17
C	137	142	132	97	106	98	4.5	5.4	5.8	36	38	32
B_2*	145	156	142	109	118	111	5.6	4.7	4	15	21	13
Sh	137	150	138	103	106	100	4.8	6.4	4.1	15	31	30
W	140	155	141	105	115	99	5.7	5	4.7	26	34	30
Gr	136	148	140	105	116	106	5.2	4.2	3.8	24	35	34
INFANTS RECEIVING GLUCOSE AND WATER												
Fi	143	135	137	106	104	101	5.4	5.1	4.7	25	23	16
Dun	135	130	126	105	100	95	5.5	3.7	4.3	10	5	5
Bl	137	138	137	111	101	100	5	4.2	4.1	16	11.8	8.7

* Twins.

water. Eight of the infants of the group receiving water were given approximately 50 cc./kg./day starting as soon as possible after birth; one received 100 cc./kg./day. On the fourth day all of the infants in both groups were given 100 cc./kg. of 5% glucose in water, their first caloric intake. The observed data for the three days with or without water are recorded in table 1. Data from Day 4 appear on some of the charts and in table 2.

Exact matching of infants receiving water and those receiving none was not possible

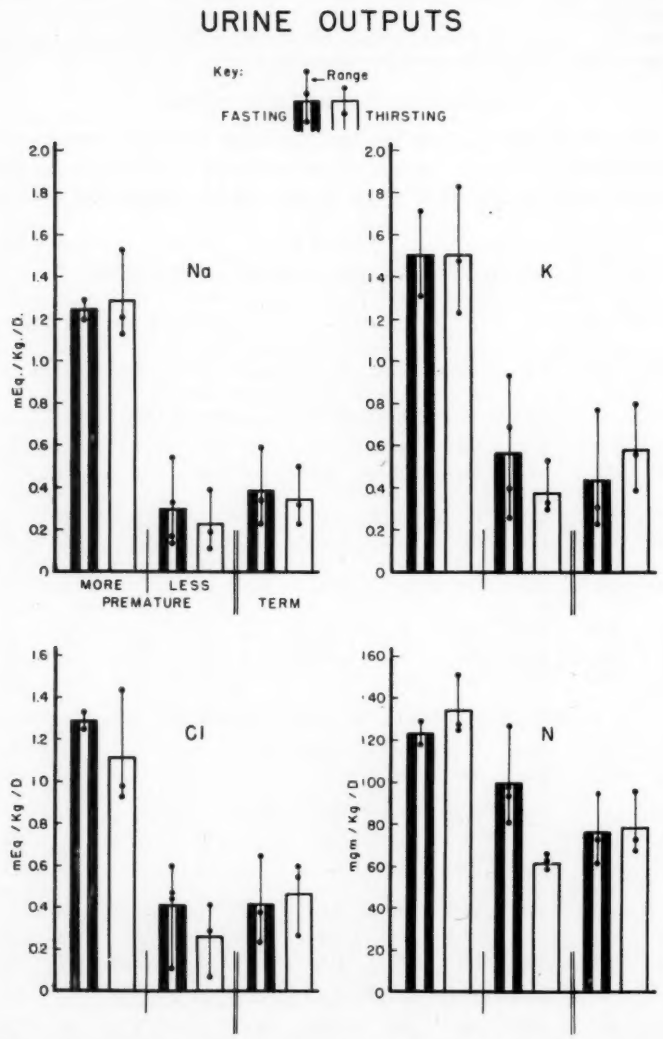

CHART 1. Average daily outputs of Na, K, Cl and N (per kg. body weight) during 3 days following birth. Infants are compared by similar gestational ages--as shown by key given beneath Na diagrams. In each gestational age group infants receiving water only (fasting) are compared with those on no intake (thirsting). Dots indicate individual infants. Data are in table 1.

except for the two pairs of identical twins. Infants were therefore selected from similar ranges of gestational age as estimated from menstrual dates, birth length and weight. As seen in table 1 this allowed division into three groups: (1) more premature, or under 36 weeks' gestation, (2) less premature, 36 to 38 weeks' and (3) full-term, 39 to 40 weeks'.

The somewhat artificial separation between groups 1 and 2 was considered justifiable because of certain findings limited to the infants of less than 36 weeks.

The results during the first three days are most conveniently presented before considering those of Day 4, which will be taken up later. As shown in detail in table 1 and

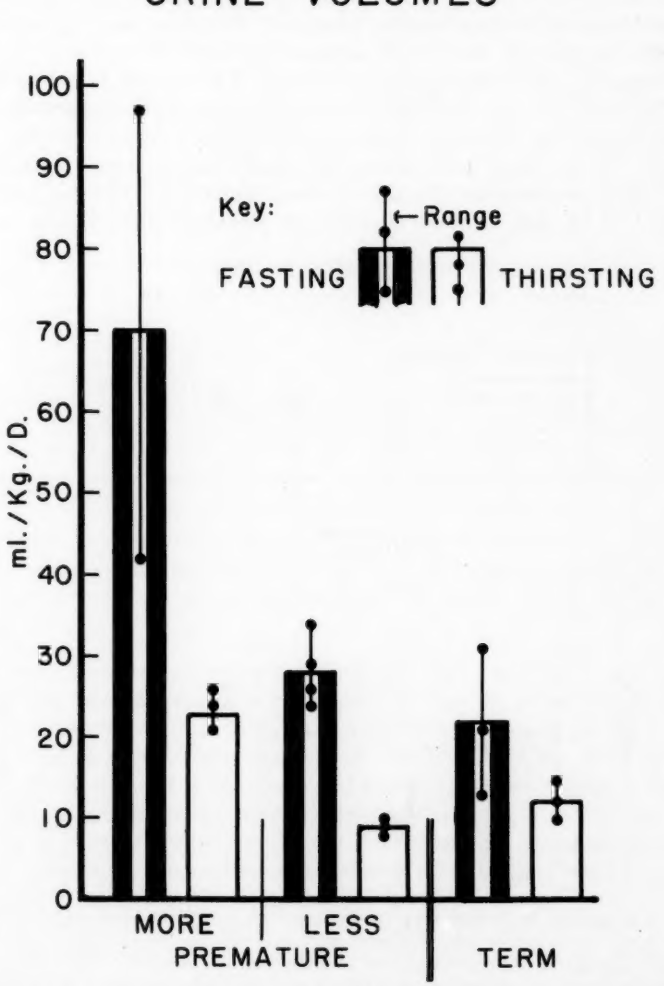

CHART 2. Average daily urine volumes (per kg. body weight) during 3 days following birth. See legends in chart 1 and table 1 for further details.

graphically in chart 1, the average daily urine outputs of Na, K, Cl and N by infants of similar gestational ages were essentially unaffected by absence of water intake. A significant and unexpected finding was the much greater output of these substances by infants of less than 36 weeks' gestation as compared to all others, whether receiving water or not.

The expected large reduction of urine volume in the absence of water intake is shown in chart 2, constructed from the measurements in table 1. It is of interest that Premature Infant T_1, who received twice the water load of the others, dealt with this without difficulty by secreting a proportionately greater volume of dilute urine. The large urine volumes of the more premature infants without water intake, which are roughly proportionate to the increased outputs of solids mentioned above, are in accordance with previously published observations from this laboratory.[3] The values found for the osmolarity of the urine, measured in the 24 hour collections, are recorded in chart 3.

The changes in serum concentrations of Na and Cl and in B.U.N. on the third day are depicted in chart 4 and the actual values listed in table 2. The infants who received water had a scattering of Na and Cl levels with a tendency toward reduction from the birth value. On the other hand, absence of intake was consistently accompanied by increased serum concentration. The highest actual figures were 162 mEq./l. of Na and 118 mEq./l. of Cl, both in members of the less premature group. During the fourth

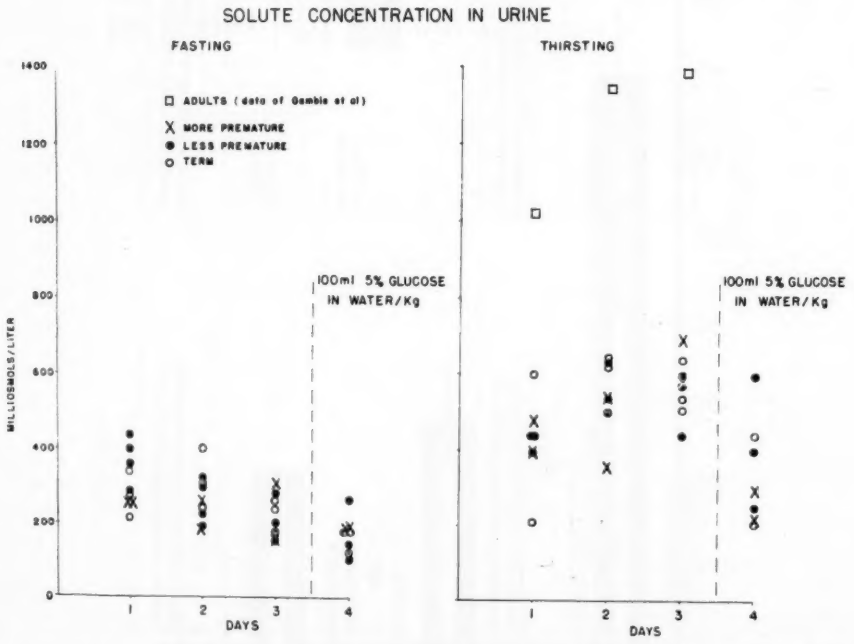

CHART 3. Osmolarity of 24 hour urine specimens collected from individual infants during 4 days following birth. Infants whose urine concentrations are charted on left received water only during first 3 days (fasting); concentrations charted on right represent urines of infants given no intake whatever during first 3 days (thirsting). All received water and glucose on Day 4. Values for thirsting adults from data furnished by J. L. Gamble.

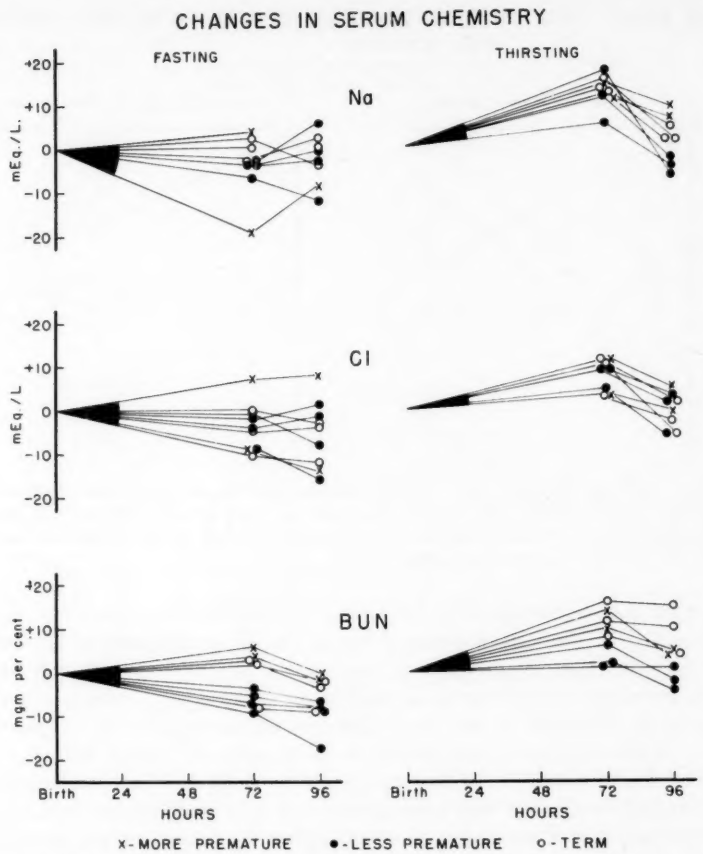

CHART 4. Changes from concentration of serum Na, Cl and B.U.N. at birth, after 3 days of water intake (fasting) or no intake (thirsting) and fourth day of 5% glucose in ±100 cc. water/kg. Data are in table 2.

day, to be discussed below, all increases were reversed after provision of water and glucose. Blood urea nitrogen concentrations rose over the three day period in several of the infants receiving water and in all of the infants deprived of water intake, the highest in that group reaching 38 mg./100 cc. on the third day. On Day 4 the values again fell. The serum concentrations of K are not charted because, as shown in table 2, these presented no significant differences between the two groups.

According to the data recorded in the first three charts the fasting newborn infant deprived of water intake manages to remove in urine the solute load which is incidental to the state of fasting (chart 1) in spite of a greatly reduced urine volume (chart 2) by adequate increase of the osmolarity of the urine (chart 3). This adjustment does not, however, completely meet the situation produced by water deprivation. Reduction of water outgo in the urine falls far short of covering obligatory water expenditures by the body, with the result that the rate of loss of body water is extensively increased over that

AVERAGE WEIGHT LOSSES IN FIRST 4 DAYS AS RELATED TO MATURITY AND INTAKE

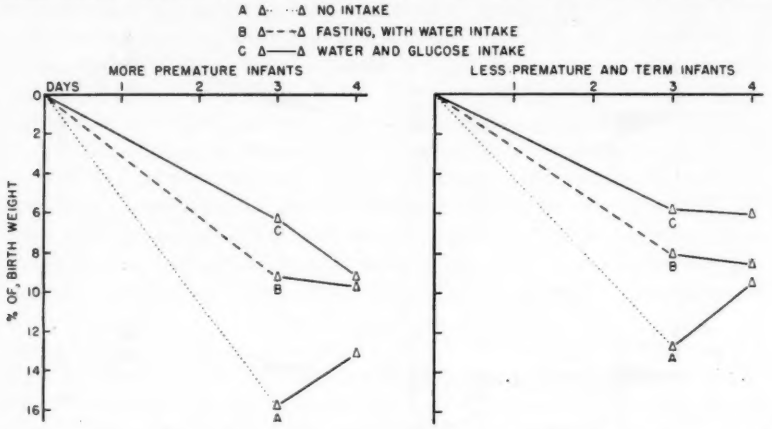

CHART 5. Average changes in body weight. Since weight changes in premature infants of 36+ weeks' gestation were similar to those of term infants, data from all were combined for diagram on right. On Day 4, all infants studied received water and glucose. Infants whose average losses are shown by lines C received water and glucose on Days 1-3 also.

found in the state of fasting where water intake is provided. This is shown in chart 5 by lines A and B indicating body weight reduction which may be taken as approximately measuring water losses. If the usual concentrations of electrolytes in the body fluids are to be preserved the increased water loss must be accompanied by a corresponding increase of removal of electrolytes in the urine. This does not occur (chart 1). Apparently the kidney is unable to remove this addition to solute outgo by further increase of urine osmolarity. The inevitable rise of concentrations in the body fluids is shown by the plasma values recorded in chart 4. This investigation thus fails to reveal any protective effect of the relatively high water content of infants against the consequences of water deprivation.

A differing response by the infants in the two groups to 5% glucose in water given on Day 4 is also shown in chart 5. The progress of the water loss found for fasting infants with water intake is almost arrested when glucose is provided (Lines B). In the group of infants first given water (with glucose) on Day 4, the reversal of lines A indicates replacement of a deficit of body water beyond the loss incidental to fasting and derived from the additional circumstance of thirsting. The correct volume of body water for an infant subsisting on water and glucose is thus promptly established, with incidental restoration of the usual concentrations of electrolytes (chart 4). The data describe the rapidly reparative effects of glucose which, in these normal infants, were almost completely gained over a 24 hour period.

The results have brought to light other points of interest. No infant's temperature became elevated and none showed any obvious clinical evidence of disturbance associated with the hemoconcentration. No entirely satisfactory reason has been found for the relatively larger outputs of Na, K, Cl and N and of urine by prematures of less than 36 weeks' gestation with or without water intake. These more premature infants may be required, because of low fat stores,[12] to consume a greater proportion of their lean body tissue during three days without caloric intake, thus releasing relatively more electrolytes

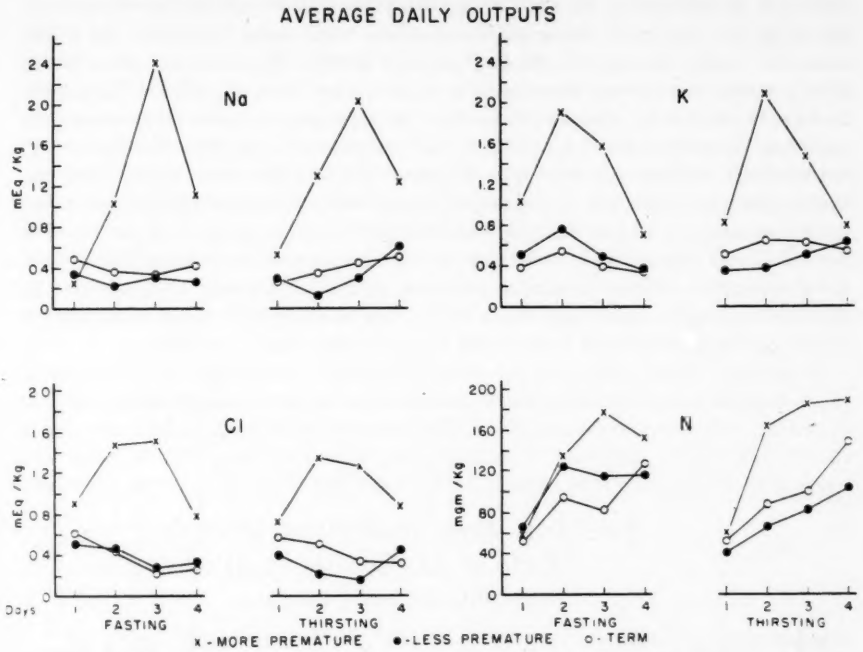

CHART 6. Average daily outputs of Na, K, Cl and N on individual days. Plotting is not cumulative; symbols for infants in 3 gestational age groups are connected only to clarify trends. (See legends of previous charts for definitions of fasting and thirsting.)

and nitrogen than might require excretion by larger infants burning more fat. Comparison of day-to-day outputs (Chart 6) is of interest in this connection. The highest value found for solute concentration in the urine, 680 mOsm./l., was from one of the more premature infants on the third day without water intake; thus, in the group of newborn infants studied no relation of osmolar concentrating capacity of the kidney to degree of prematurity was apparent.

COMPARISON WITH ADULTS

To compare the findings from newborn infants with the effects of similar circumstances in adults is difficult. In the newborn infant, the restriction of intake to water alone, or to nothing whatever, is simultaneous with the removal of the organism from the placenta as its organ of excretion; in the adult subject, the single abrupt alteration is that of intake. Because the adult adjusts outgo slowly to any such change, metabolic data obtained from adults during the first portion of study periods are conventionally omitted from consideration. Thus in Gamble's studies of life-raft rations[6, 13, 14] the last four days of six day fasting periods and the last three days of four day thirsting periods were selected for analysis. The results of the present investigation are thus not strictly comparable in point of timing. With these reservations as to the validity of the comparison, a large difference in the relation of electrolyte to water losses is shown in chart 7.

Since water expenditure is quite closely a function of body surface, which for the infant at birth is about twice as large per unit of mass as is the surface of an adult, the

data used in constructing the chart are recorded per unit of surface. On this basis, as shown in the right hand section of the chart the water losses by infants and adults, measured roughly by body weight loss, are approximately the same; the losses during fasting without water being about twice as large as when water is provided. In contrast, as shown in the left hand section of the chart, the accompanying losses of the structurally important electrolytes, Na, Cl and K, by the less premature and term infants are very much smaller per unit of surface than the losses by adults. The losses by the more premature group are larger and in the state of fasting with water intake approach the values found for adults. The data from the adults describe a large extension of the losses of Na and Cl and a considerable increase of loss of K along with the increased loss of body water under the additional circumstance of thirsting. This adjustment is not displayed by the newborn infants; as already shown by the data in chart 1 the outgo of electrolytes found for fasting with water intake is not increased when water is withheld.

It has been demonstrated that for adults the normal concentration of electrolytes in the body fluids is preserved by a closely parallel loss of water and electrolytes in the state of fasting, with or without water intake. The losses of electrolytes by adults recorded in chart 7 thus describe the extent of withdrawal of electrolytes, along with the water loss, required to defend body fluid concentrations. Water loss being the same for adults and

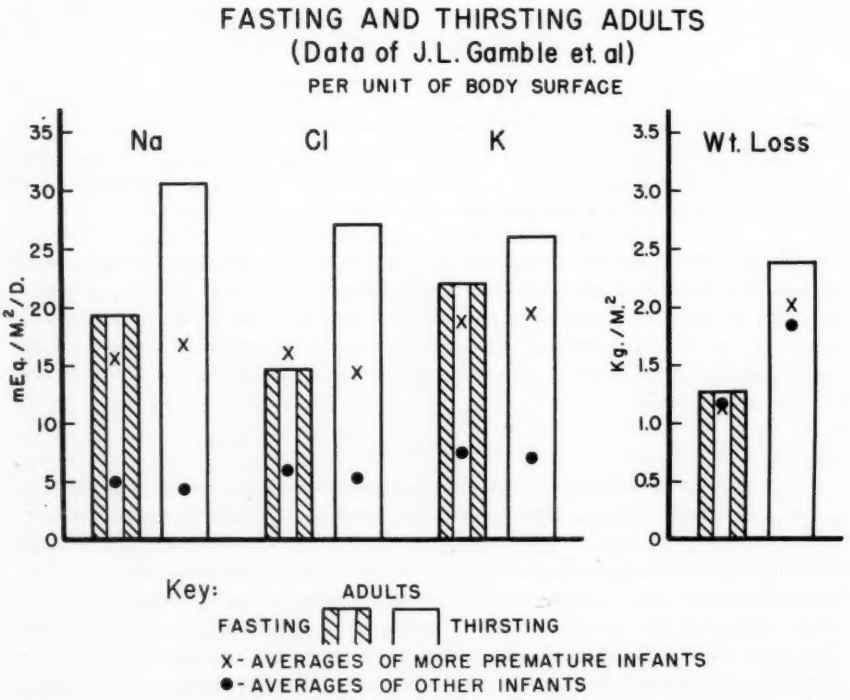

CHART 7. Average daily urine outputs of Na, Cl and K, and weight losses, of normal adults during 3 days of fasting (water intake only) or thirsting (no intake). Columns represent adults,[6, 13, 14] and crosses and dots represent averages of infants in present study. All data presented per square meter body surface.

infants on the basis of reference used in the chart, the much smaller loss of electrolytes found for the infants quite clearly implies inadequate removal and, in consequence, increased concentration of electrolytes in the body fluids. The plasma values recorded in chart 4 describe the expected increase of concentrations during the three days of fasting without water. It would also be expected that infants with water intake, and losing body water at one-half the rate found when water is withheld, would exhibit a smaller but measurable increase of concentrations. No increase was found; the scatter of the individual measurements on the third day (left hand side of chart 4) describes the usual extent of oscillation. Their average value is closely the same as the average of the measurements at birth. Perhaps a much larger series of measurements would define a small average increase of concentrations. The curious finding of widely different quantities of electrolytes removed in the urine of adults and newborn infants in relation to loss of body water during

TABLE 3

DAILY LOSSES OF ELECTROLYTES PER LITER OF BODY WATER LOST BY FASTING SUBJECTS WITH AMPLE WATER INTAKE

	Na m.mol./l.	Cl m.mol./l.	K m.mol./l.	N gm./l.
Adults (Data of J. L. Gamble)	71	53	80	25
Infant* (1 mo.)	82	76	95	14
Newborn Infants (term) (Calculated from table 1)	18	21	20	4

* The authors are indebted to W. M. Wallace and J. Metcoff for permission to include these data from an unpublished study.

fasting with an ample water intake is shown again by a simple approach in table 3. Here the daily losses of the electrolytes are referred directly to the loss of body water.* The table includes data from a month old infant, which are in approximate agreement with those from the adults and are about four times larger than the values found for the newborn infants.

The apparent explanation of inadequate removal of electrolytes in relation to water would seem to be a lag in renal response to the solute load claiming excretion during fasting. With the large urine volume provided by ample water intake there was no obstacle to increase of urine concentration; as shown in chart 3 total osmolarity was well below that in the urines of infants denied water, and moreover over the three day period the concentration declined instead of increasing. Actually the osmolarity of the urine is approximately that of the blood plasma, but when the volume of urine in the infants given water is extensively reduced by withholding water it is immediately evident that the kidney is capable of secreting urine which is hypertonic to the plasma. The total amount of solutes excreted, however, is not increased in the presence of demand for additional removal of the electrolytes produced by a loss of body fluid which is twice as large as the loss found when water intake is provided.

* The values for water loss were derived from measurement of body weight loss corrected for weight of body protein and fat oxidized estimated from urine nitrogen on the basis of an energy expenditure of 60 cal./kg./day.

Effects of Glucose Given from the First Day

The water-saving effect of the glucose given on Day 4 following three days of fasting with an ample water intake is clearly shown in chart 5, and has been referred to above. In order to observe the effect of providing glucose along with water over the first three days, seven infants were studied. Glucose was given in 2.5 to 10% solutions, administered orally in amounts approximating 50 cc./kg./day. On Day 4, also, all received 100 cc./kg. of 5% glucose in water.

As shown by the measurements of body weight loss in table 1 and by lines C in chart 5, the loss of weight over the first three days was much less when glucose was given. For the more premature infants weight loss was reduced from 9.2% to 6.3% of the birth weight and for the group including less premature and term infants the reduction of weight loss was from 8% to 5.8%. The results of this study again describe conservation of body water when glucose is provided. This outcome was expected, but the sparing effects of glucose on body protein and electrolytes which have been demonstrated for adults[6] and children,[15] and therefore were also expected, are not visible in the data from the seven infants. The absence of these effects, which are large in adults, is puzzling. If the relatively anaerobic metabolism presumed to follow birth[16, 17] reduces the energy provided by glucose to a degree interfering with sodium- and protein-sparing, the effect of glucose feeding upon weight loss should be prevented also.

The relatively larger loss of body water than of electrolytes observed in the newborn infants suggests an explanation of the absence of demonstrable sparing of the electrolytes when glucose is given. Relative water deficit would obviously be increased by further conservation of electrolytes. What the situation needs is conservation of water and this effect is clearly exhibited when glucose is provided. In other words in the presence of a surplus of electrolytes in body water, the kidney should continue, as it does, to remove them at such rate as its functional capacity permits. In any case, the data suggest a clinical advantage in the conservation of body water as a result of substituting glucose solution for plain water intake in the immediate postnatal period.

Summary and Conclusions

These studies were undertaken primarily to evaluate the importance of fluid intake soon after birth and to determine whether consequences of its omission are modified by the relative excess of water in the body of the newborn infant. Weight losses, outputs of Na, K, Cl, N and water, and serum concentrations were investigated in nine infants receiving no intake for 72 hours after birth and in nine controls receiving approximately 50 cc. water/kg. daily. In seven other infants, 2.5 to 10% glucose was added to the water intake of the first three days.

The results can be summarized as follows:

1. The amounts of electrolytes and nitrogen excreted in the urine were unaffected by water intake. Thus, infants of 36 weeks or more in gestational age excreted averages of about 0.3 mEq. of Na, 0.45 mEq. of K, 0.35 mEq. of Cl and 80 mg. N/kg. daily during three days after birth, whether or not water was provided. The average weight loss of 13% in three days without water intake as against 8% when water was given indicates the greater loss of body water necessitated if fluid is withheld.

2. Five infants of less than 35 weeks' gestational age excreted amounts of electrolytes 2 to 3 times larger (and somewhat larger amounts of nitrogen) per kg. of body weight than did the more mature infants. Again, the excretions were uninfluenced by water

intake. The weight losses of these more premature infants were increased by omission of water intake to about the same degree as in the less premature or full-term ones similarly restricted.

3. In infants of all gestational ages studied, omission of water produced a rather uniform increase in urine concentration; the highest osmolarity of 680 mOsm./l. on the third day was in the urine of a premature infant. Concentrations of Na and Cl in the serum, and of B.U.N. rose in all infants not receiving water, again without regard to maturity.

4. The measurements obtained from infants were compared on the basis of surface area with values which have been established for adults. On this comparison, daily losses of body weight, and thus of body water, were approximately similar for infants and adults during fasting with and without water intake, but outputs of electrolytes by the infants were relatively reduced.

5. The provision of water and glucose to infants, either on the fourth day following birth, or instead of water alone during the first three days, resulted in conservation of body water, but no sodium- or nitrogen-sparing was demonstrated.

While possible explanations of these various results are considered above, it seems reasonable to draw a few broad and clinically applicable conclusions here. The composition of the infant at birth affords no protection against the chemical consequences of water deprivation. Age-conditioned limitations in concentration of urine result in inefficient conservation of body water and, therefore, in the occurrence of hemoconcentration before it would take place in the adult. Although thus unable to maintain homeostasis, the clinically satisfactory status of the infants studied and their prompt return to normal serum concentrations after one subsequent day of water and glucose administration suggests their tolerance of three days without water intake. When fluid is given during the immediate postnatal period, the results of this study suggest that body water will be conserved if the fluid be glucose solution rather than plain water.

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SPANISH ABSTRACT

Efectos del Ayuno en el Período Post Natal Inmediato

Se considera como causa importante de morbilidad y mortalidad en los recién nacidos, la inhalación de alimentos o de contenido gástrico, particularmente en prematuros o en recién nacidos con alteraciones respiratorias, hemorragia cerebral, edemas o anormalidades congénitas que complican y hacen más difícil su adaptación a la vida post natal. Con el ayuno de alimentos y líquidos tanto a prematuros como a nacidos a término, los autores han observado disminución en la frecuencia de trastornos pulmonares y evolución normal de los niños. Esta tolerancia a la restricción de líquidos les ha sugerido la idea de que el mayor contenido acuoso del recién nacido constituye una reserva para las necesidades excretoras, superior a la de individuos de mayor edad. El presente trabajo se realizó con el fin de probar esta hipótesis y determinar si la administración de agua influye significativamente en la eliminación de electrolitos y nitrógeno en la orina y en su concentración en diversos líquidos del cuerpo. Asímismo se estudió en otra serie de niños a quienes se les administró agua y glucosa, si ésta produce en los recién nacidos el efecto de ahorro de potasio y sodio demostrado por Gamble en los adultos.

Se investigaron las pérdidas de peso, la eliminación de sodio, potasio, cloro, nitrógeno y agua y sus concentraciones séricas en nueve niños con ayuno de 72 horas después del nacimiento y en nueve niños control que recibieron aproximadamente 50 c.c. de agua por kilo de peso y por día. A otros 7 niños se le agregó al agua de los primeros tres días, una cantidad de glucosa variable de 2½ a 10 gramos por ciento.

Los resultados obtenidos fueron los siguientes:

Las cantidades de electrolitos y nitrógeno excretados en la orina no fueron afectadas por la ingestión de agua, es decir, las cifras obtenidas fueron las mismas en los dos grupos estudiados.

La pérdida de peso promedio de trece por ciento en los niños con ayuno comparada a la de ocho por ciento cuando se administró agua demuestra la mayor pérdida de ésta durante el ayuno. Cinco niños menores de 35 semanas de edad intrauterina excretaron cantidades de electrolitos por kilo de peso de dos a tres veces (y aún mayores por lo que respecta al nitrógeno), que niños de más edad, sin que las excreciones fueran influídas al administrárseles agua. La pérdida de peso de los niños más prematuros fué mayor con el ayuno, pero semejante a la del grupo similar de los nacidos a término y prematuros de más edad intrauterina.

Se observó un aumento uniforme en la concentración urinaria, y concentraciones mayores de sodio, cloro y nitrógeno ureico en el suero sanguíneo de los niños en ayunas, sin relación a su grado de maduración. La pérdida diaria de peso y del agua es similar para niños y adultos en ayuno sin ingestión de agua, pero la excreción de electrolitos por los niños se encuentra relativamente reducida. La administración de agua glucosada a los niños, bien fuera al cuarto día del nacimiento o en substitución de agua sola durante los primeros días, produjo retención acuosa pero no se pudo demostrar ningún efecto ahorrador de sodio y nitrógeno.

De estos hechos se pueden obtener algunas conclusiones de aplicación clínica. La composición

del niño al nacer no le proporciona protección contra las alteraciones químicas causadas por el ayuno de agua; las limitaciones producidas por la edad en cuanto a la concentración de orina, producen una conservación defectuosa del agua corporal y por lo tanto hemoconcentración más rápida que en el adulto. A pesar de esta incapacidad para mantener su equilibrio hídrico, existe tolerancia de los niños recién nacidos al ayuno de agua por tres días. Y por último nuestras observaciones sugieren que se mantendrá el agua corporal si se le da al recién nacido durante el período inmediato post natal, una solución glucosada en vez de agua sola.

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EVALUATION OF THE SKELETAL AGE METHOD OF ESTIMATING CHILDREN'S DEVELOPMENT

I. Systematic Errors in the Assessment of Roentgenograms

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THE assessment of children's development and state of health by roentgenographic atlases of skeletal maturation, especially the hand atlas of Todd[1] and its successor, the Greulich-Pyle atlas,[2] is becoming increasingly common—for example, in group nutrition studies, in examining a child of poor physique, in controlling endocrine therapy and in predicting a child's adult stature (Bayley and Pinneau[3]).

By comparing a child's hand roentgenogram with those in an atlas an observer estimates the child's skeletal age, which is the average age (more exactly, the modal age) of the selected healthy (atlas) children whose hands were at the same stage of development as the hand that is being assessed. When, as is commonly found, the various parts (carpals, epiphyses and shafts) in the observed film do not all agree with any one of the standard RGs, the mean of the skeletal ages of all the parts is usually taken as the skeletal age of the hand.

Problems of normal variation and the applicability of Cleveland children's standards to other groups are discussed in the Greulich-Pyle atlas. Insufficient attention, however, has been paid to observational error in the assessments, which is a question of growing importance, because users of the method are no longer only those who have had contact with Todd, his collaborators or successors. An assessor can be anyone (pediatrician, endocrinologist or nutritionist) who obtains a copy of the Greulich-Pyle atlas.

The existence of error is commonly recognized, but its magnitude is seldom estimated or analyzed. Thus, Bayley and Pinneau[3] wrote recently: "X-rays may be inaccurately read. Accuracy can be increased by practice in the use of the standards, but such assessments always remain approximations. It is, therefore, very desirable to reduce the error by making several independent readings (by the same or different persons) and then to take the average of these readings." Here, the variation between observers and the variation within observers are run together, but they may be very different. Moreover, if a method is to be of much use some reliable numerical quantity, whether $\pm$ 1 month or $\pm$ 1 year, must be affixed to the term "approximation."

Some observers test their skill by asking an expert to read a few films that they have

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assessed, but this is not practicable for many workers and it can lead to a biased estimate. Any estimate should be expressed in a form directly applicable to the observer's other (routine) assessments, not by such quantities as the coefficients of reliability quoted by Todd.[1] Even a statement such as "Assessors of greatly unequal experience readily assess the maturity of skeletal roentgenograms within a six-month divergence" (Todd[1]), is not sufficiently specific; furthermore, this statement was, apparently, based on only eight students, all instructed by Todd.

Recent tests of common technics in hematology (Biggs and MacMillan[4]), clinical chemistry (Belk and Sunderman[5]) and thoracic x-ray diagnosis (Birkelo and others[6]) have revealed a disturbing degree of error. Skeletal assessment, although developed from prolonged, minute and accurate morphologic observations, is a relatively new method, and it would be unfortunate if its claims were overstated through ignorance of its errors. Hence it would seem desirable to explore those errors, even if the results cast doubt on the authors' own observational skill.

Types of Observational Error

As in all observational methods, two types of error should be distinguished: (1) systematic and (2) variable.

Systematic Error (Error of Bias): This can be defined in skeletal assessment as the persistent difference between an observer's assessments and the assessments of the same RGs by an expert, preferably the expert who devised the atlas. Such a comparison of assessments on a series of films would give (1) a mean systematic error of plus or minus so many months, and (2) a statement of variation in the observer-expert difference among the different films, expressed most usefully as a standard deviation. This is the type of error for which allowance should be made in deciding whether the skeletal age of a child, or the mean skeletal age of a group of children, is below (or above) the atlas standard, and also in using the tables of Bayley and Pinneau[3] for the prediction of adult stature. More generally, the systematic difference between any two observers can be expressed in the same way, for use in comparing groups of children assessed by different observers, or when different observers assess RGs taken at different ages from the same child.

Variable Error (Fluctuating or Random Error): This is represented by the differences between independent assessments made by the same observer using the same atlas on the same RGs, when repeated assessments show no persistent tendency to increase or decrease. Allowances for this type of error should be made when the successive films from the same child have been assessed by the same observer to compare the progress in skeletal age and chronologic age.

The term "independent assessments," which will be used repeatedly, means assessments made without knowledge of a previous assessment of the same RG, or of the assessment of another RG from the same child, or of the chronologic age of the child, or of other information such as the child's stature.

Purpose of the Investigation

The work to be discussed here was concerned primarily with systematic error; and its purpose was threefold:

1. To see how an observer, despite lack of contact with experts, might compare himself with them and with other observers, in order to estimate his systematic error.

2. To seek for possible causes of systematic error.

3. To compare different expert assessments with each other. (The investigation is not concerned with the difference between skeletal and chronologic age.)

Macy Series of Roentgenograms

The best way to enable observers to estimate their systematic errors would be the distribution of sets of RGs multiplied as transparent reproductions of a master set assessed by an expert. This would be expensive, and there are available in Macy's[7] *Nutrition and Chemical Growth in Childhood* (vol. 2) actual-size reproductions of 90 hand RGs from 24 children, along with the skeletal age estimated on 78 of the RGs, from 18 of the children, by Todd, Francis and Pyle from the standards in Todd's atlas. The reproductions are not as clear as actual films; but they seemed worth investigating for possible general use. In 1947, therefore, after one of the authors (RBM) had learned the technic from Todd's atlas and had assessed the actual films of 150 children, she tested herself on the Macy series.

Methods

Unbiased Assessments: In this and every subsequent test the procedure* adopted to secure unbiased assessments was as follows:

On each page where RG was to be assessed another person (technician or secretary) covered the information regarding the name and age of the child with opaque paper fastened by paper clips, and wrote on the paper only the page number and the child's sex. The RGs were assessed in strictly random order (by using random numbers—Mainland[8]) to avoid bias from such causes as: (1) the influence of an immediately preceding assessment, since adjacent RGs are generally from the same child; and (2) change in the error from fatigue, increasing experience or other causes.

Repeated Assessments: Several months after assessing all the Macy RGs that were sufficiently clear for the purpose, RBM reassessed them all, in a different random order and without knowledge of her previous assessments. Her assessments were then compared with those of Todd, Francis and Pyle, which will be referred to as the "Todd" or "T" series, for the contributions of the 3 assessors cannot be distinguished. In 1951 RBM assessed the Macy RGs by the Greulich-Pyle atlas, making 2 independent readings as before.

Since volume 3 of Macy's *Nutrition and Chemical Growth* contains Pyle's assessments for 11 of the children by the new atlas, there can be presented here for 62 RGs (from 10 children) the comparison of RBM's assessments with those of Pyle, referred to as "GP" assessments to avoid confusion with "P," the symbol for "probability." Results of the earlier comparison (RBM versus T) on the 78 RGs from 18 children will be inserted where appropriate.

Technic of Assessing: Although RBM tried to apply exactly the instructions in each atlas (except that she avoided knowledge of the chronologic ages) she found it difficult to apply intelligently Todd's[3] "principle of assessment . . . the utilization of the most advanced centers," with "reservation on carpal bones and epiphysis of radius" and "greatest reliance upon metacarpal and phalangeal epiphyses." She therefore took the arithmetic mean, to the nearest month, of the stages reached by all the various maturity indicators.

A second difficulty was that some of the indicators in Todd's atlas remained unchanged for 18 mo. or more. To avoid giving them too much weight RBM adopted certain conventions; e.g., if an indicator in the atlas did not change for 24 mo. it was ignored unless its stage of development in the RG under assessment was completely above or below the stage reached by any other indicator in that RG, and then its value nearest to those of the rest was recorded and used in the averaging.

These difficulties did not arise with the Greulich-Pyle atlas. With that atlas the mean value was

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* If a reader contemplates testing himself on the Macy series for comparison with RBM or with the experts (see p. 125), in order to avoid bias he should not inspect that series or the assessments in volumes 2 or 3, either when reading this article or later, until the Macy pictures have been prepared as described in the text.

again found, as was done by Pyle in the assessments recorded by Macy. This averaging tends to overweight the 5 sets of finger bones, which repeat each other to a considerable extent; but there is not yet any satisfactory method of giving them their appropriate weight. (The average skeletal age can be supplemented by a statement of the stages reached by the most advanced and the least advanced of the indicators. The authors' observations on this are to be reported later.)

Statistical Analysis

Because of the complexity of the data (different numbers of RGs and at different ages in each child), a simple method of estimating RBM's systematic error, such as taking an average and standard deviation from all the RGs, was not justified. Therefore the analysis was more elaborate than an observer would generally need in estimating his own error from a set of films, and technical details will not be shown here. For statistical readers, however, a summary of the technics is necessary.

In analyzing data such as those of table 1 it could not be assumed that RGs numbered 1, 2, 3, etc., in one child corresponded in any way, except time order, to those bearing the same numbers in other children. Therefore the tables from the 10 children could not at the outset be combined in one large table. Instead, each table was analyzed separately, and then the resulting probability values were combined.

Each of the 10 tables was subjected to analysis of variance, the triple interaction being used as the error term. Where variance ratios had one degree of freedom, the probability of the equivalent t was found by interpolation in Hartley and Pearson's table.[9] To allow for the direction of a difference, as from +1.17 to −3.33 in table 1, single-tailed probabilities were used (Fisher[10]). When the degrees of freedom between classes were greater than unity the probabilities for the variance ratios were found by Simaika's[11] method of interpolation in Thompson's[12] table of percentage points of the incomplete beta-function. The probabilities derived from the 10 children were combined by conversion of each probability into chi-square for 2 degrees of freedom and summation to give chi-square for 20 degrees of freedom (Fisher[13]).

This general analysis was supplemented, where desirable, by analysis of parts of the data. In all analyses the usual criterion of significance was adopted, i.e., P less than 0.05, where P is the probability of occurrence of an observed value (such as a difference) or a greater value than the one observed, if chance alone were operating.

Comparison of RBM with Experts

Table 1 shows RBM's systematic errors on the RGs of one child. A positive value indicates that her assessment was higher than that of the expert, a negative value indicates

TABLE 1

Example of Data for Comparison of RBM's Assessments with Expert Assessments (Hand RGs of Bobby)

(R[1], R[2] indicate first and second readings)

RG No.	Chronologic Age (mo.)	RBM's Assessments Minus Expert Assessment (mo.)				Mean of 4 Differences
		Todd's Atlas		Greulich-Pyle Atlas		
		R(1)	R(2)	R(1)	R(2)	
1	65	−3	+6	−3	−4	−1.00
2	71	+7	+10	+3	−3	+4.25
3	73	+7	+7	+1	−5	+2.50
4	87	−3	−2	−10	+2	−3.25
5	113	−15	−6	−12	−3	−9.00
6	150	+5	+1	−3	−3	0.00
		Mean = +1.17		Mean = −3.33		

the reverse. A similar table was prepared for each of the other nine children in whom a comparison with both T and GP was possible. In the 10 children the number of RGs per child ranged from 3 to 10, and totaled 62.

Analysis by the methods summarized above provided clear evidence on five points: (1) differences between readings on the same RG; (2) average systematic errors; (3) differences in systematic error between the atlases; (4) differences in systematic error between RGs from the same child; (5) differences in the systematic error between children.

1. Differences between Readings on the Same Roentgenogram: Throughout the whole series of readings in both the T and GP comparisons there was no significant tendency for the first reading to give a larger or smaller systematic error than the second reading of the same RG with the same atlas. The probability, P = approximately 0.5, was what one would expect if nothing but chance determined whether the first or second reading would show the larger error. Therefore:

(a) There is no reason to doubt that RBM had developed a stable system of assessing, whatever might be the magnitude of her systematic error.

(b) The two readings on each RG can be considered as strict duplicates for the estimation of random or variable intrafilm error, to be discussed in a later report.

2. Average Systematic Errors: For the value RBM—GP, the means in the 10 children ranged from −8.4 to +2.5 months. Six of the eight negative values were significant, whereas the two positive values were not; and combination of the probabilities left no doubt of an over-all tendency for the error to be negative. Similar results were obtained from the comparison with Todd's assessments; and RBM had, therefore, a decided tendency to estimate skeletal ages lower than did the experts. In the Todd comparison this might be attributed to the method of averaging used by RBM in place of Todd's emphasis on the more advanced centers; but this would not account for the same tendency in the GP comparison, because Pyle's assessments, like those of RBM, were averages of all indicators.

3. Differences between Atlases: Although RBM's mean systematic errors were similar in the T and GP comparisons, a significant difference was found, namely, that her assessments tended in general to be farther below (or less far above) the GP assessments than with reference to the T assessments. Examples, showing mean systematic errors in months, are:

Bobby: RBM − T = +1.17; RBM − GF = −3.33
Herbert: RBM − T = −6.25; RBM − GP = −8.375
Phyllis: RBM − T = +2.17; RBM − GP = +1.67

Although there were two exceptions to this rule, they did not counteract the evidence of the other eight, for the combined probability was less than 0.001.

This difference could not be attributed to the fact that the Greulich-Pyle atlas, by more exclusive selection of RGs from healthy children, had raised the standards of skeletal age; because with each atlas the comparison was between RBM's assessments and those of the expert using the same atlas. It might, perhaps, be explained by a change in her interpretation between the time of her Todd assessments and the time of her Greulich-Pyle assessments; but, whatever the cause, it shows that an observer should not assume that his systematic error will remain the same, even if the only change in the system of assessing is a revised atlas.

4. Differences between Roentgenograms from the Same Child: Both in the GP comparisons (10 children) and in the T comparisons (15 children from whom two or more films

were available) RBM's systematic error differed significantly between RGs from the same child (P less than 0.01). This meant that the systematic error estimated for any one film was no guide to the error in another film from the same child. Moreover, the differences between the two systematic errors, RBM — T and RBM — GP, also varied significantly between different films of the same child (P less than 0.01).

5. Differences between Children: In both the T and GP comparisons RBM's systematic error varied significantly more between children than between RGs from the same child (P less than 0.001). Therefore the average systematic error estimated from one child was no guide to the average systematic error for the assessments on any other child.

Causes of Differences in Systematic Error between Roentgenograms and Between Children: In the search for possible causes of these two unexpected differences, two features were explored: (1) quality of RG; (2) age differences.

1. Without recalling her assessments, RBM classified all the Macy roentgenograms as "good," "fair" or "poor," chiefly according to their clarity and partly according to their completeness (exclusion of finger tips in some of them). No association between quality of RG and size of systematic error was found. Sometimes the "worst" picture in a child's series gave a small error and sometimes the "best" picture gave a large error.

2. Difficulty in assessment is known to be greater at certain ages than at others, but no association between age and magnitude of the systematic error was detected.

At present, therefore, one can merely speculate regarding causes, and the authors' speculations have centered on the fact that RBM's assessments were all independent, i.e., made without any information about the child except sex. This is apparently not the customary method. The Greulich-Pyle atlas assumes that the chronologic age is known before assessment, and it is believed that, as in most other radiologic diagnoses, previous RGs are often examined during the assessment of the latest film.

It is not known what information was possessed by the experts who assessed the Macy series, and, in any case, the authors' speculation does not impute conscious bias to them or to other observers; but it should be recognized how readily additional knowledge can affect an assessment. The authors have noticed that after RBM has estimated the skeletal age from a RG for diagnostic purposes, when she learns the chronologic age, or her assessment of a previous RG from the same child, or some other information such as retardation in stature, she is liable to wonder whether some features that contributed to her estimate should have been interpreted differently.

Such knowledge, therefore, if possessed before an assessment was made, might easily affect the assessment, despite every effort at objectivity. Consequently, all the assessments of a particular child's RGs would to some extent be related to each other. If another observer's assessments were strictly independent, some of them might differ from those of the first observer much more than other assessments in the same child; and there would be an interfilm variation in systematic error. Further, the influence of the additional knowledge might differ in degree and even in direction (elevation or depression of assessments) in different children; and this would account for the differences between children in the systematic error of someone who assessed all RGs with strict independence.

It will be seen later that this speculation receives some support from the comparison of two expert assessments of the same RGs; but even if experimental proof were obtained it might still be argued that the best assessment is made when most is known about the child, just as it is often said that a radiologist should take into account clinical history and present symptoms. This latter belief is itself questionable in view of radiologists' fluctuations in diagnosis on independent reassessment of the same chest films (Birkelo

and others[6]). Certainly in the appraisal of a child it seems desirable to make all judgments, including those on skeletal maturation, independent of each other, and then collate them in a final judgment.

Estimation of Systematic Errors for Routine Use

The foregoing analyses show the precautions necessary in finding the three types of information on systematic error that are commonly needed: (1) The mean error in the survey of a group, with one RG per child; (2) The possible error in the assessment of a single RG; (3) The possible error in the assessment of the progress of an individual child.

The third item will be considered later. Estimation of the first two items requires a series of children, each providing one RG, because it has been shown that in the Macy

TABLE 2

Randomly Selected RGs from 10 Children in Macy Series (One RG per Child) to Show RBM's Systematic Error with Greulich-Pyle Atlas

(Serial numbers indicate position, in chronologic order, of RG in hand series for child named)

Name of Child	Serial No. of RG	Systematic Error (RBM-GP) in Months		
		First Reading	Second Reading	Mean
Billy	4	−10	−5	−7.5
Bobby	2	+3	−3	0.0
Donald	3	−3	−6	−4.5
Frank	7	−5	−4	−4.5
Herbert	1	−7	−11	−9.0
Jimmy	5	0	−3	−1.5
Barbara	7	+10	+10	+10.0
Betty	5	−9	−7	−8.0
Jean	1	+1	+6	+3.5
Phyllis	1	+4	+3	+3.5

series multiple RGs from one child did not provide an estimate of the variation in systematic error found among different children. The authors' sample of 10 children, or even the sample of 18 used for comparison with Todd, is too small because of the large variations that were found; but it is illustrative and also makes it possible to estimate the size of sample needed.

Mean Systematic Error: Table 2 shows the estimates of RBM's systematic error on 10 RGs, one film having been selected from each child by a table of random numbers. Because in routine assessments an observer may be unwilling to assess the films twice at a sufficient interval, the first reading was used as if it were the only one, and the following values were obtained:

Mean systematic error (RBM − GP) from 10 films = −1.60 months.

Standard deviation of series of 10 = 6.36 months.

Standard deviation of mean = 2.01 months.

Therefore $t = 1.60/2.01 = 0.80$, and P is between 0.4 and 0.5; i.e., the mean does not differ significantly from zero. All that can be said (by use of Fisher and Yates' Tables[14]) is that there is a 95% probability that the mean systematic error lies between −6.15 and

+2.95 months. In the Todd comparison a sample of 18 RGs (one from each child) gave similar results.

Analysis of the full series has already shown indubitable evidence of a negative systematic error; but because the error varies so greatly between children these samples (of 10 and 18 children, each contributing one RG) were too small to demonstrate that the mean error differed from zero.

Much greater precision in the estimate of the mean error than is shown here is desirable and this can be sought in two ways: (1) by taking more than one (independent) reading of each RG and using the average of these replicates, and (2) by increasing the number of RGs, which, as already stated, implies increasing the number of children, each child still contributing only one RG.

1. Duplicate Readings: When the means of duplicate readings in table 2 were used, instead of only the first readings, the changes were small:

Mean of 10 systematic errors (RBM − GP) = −1.80 months instead of −1.60 months found from single readings). Standard deviation of series = 6.11 months (instead of 6.36). Standard deviation of mean = 1.93 months (instead of 2.01).

The 18 RGs used in the RBM − T comparison again gave similar values. There is, therefore, very little to gain from duplicate readings, and to take three or more readings would be a waste of time. (To ascertain his stability of assessment by estimating his variable error an observer must, however, at some time make a series of duplicate readings.)

2. Increased Numbers of Children: To reduce the standard deviation of the mean systematic error the number of RGs (i.e., of children) must be increased, for the standard deviation is found by dividing the standard deviation of the series by $\sqrt{N}$, where N is the number of RGs. The authors' estimates of the standard deviation of the series in both the T and GP comparisons are a little over six months. For illustration we shall suppose that an observer's estimate from 50 children is 7 months, and that his mean systematic error is −3 months. The standard deviation of the mean is then $7/\sqrt{50} = 1$ month approximately, and the 95% confidence limits of the mean, given by ± twice the standard deviation, are $-3 \pm 2 \times 1$, i.e., −5 and −1.

If the observer then surveys a group of children and estimates their mean skeletal age anywhere from 1 to 5 months below the atlas standards, he can consider the difference sufficently explained by his systematic error; that is, the expert, using the same atlas, might well have assessed the children as being, on the average, up to the standard. (If, however, the difference is outside the range −5 to −1, either above or below, the observer should, by using Fisher's t test, compare this series of assessments with the sample of 50 from which he estimated his error.)

If there were 100 films in the test series, with a mean = −3 months and standard deviation of series = 7, the standard deviation of the mean would be $7/\sqrt{100} = 0.7$, and the confidence limits of the mean would be −4.4 and −1.6 months.

Even if the precision of observers in general were no greater than the authors have supposed (standard deviation for individual assessments = 7 months) the above estimates would, it is thought, sufficiently justify the assessment method for surveys of groups, because then the sample size compensates for the individual variation.

Variation between Single Roentgenograms: In the assessment of an individual RG the sample size does not compensate for variability, as in the survey of a group, and the standard deviation from a series of test films must be used directly. In the RBM − GP comparisons (10 films with one reading on each) this standard deviation was 6.36 months.

This might, of course, differ greatly from the "true" standard deviation that would be approached by taking a very large sample; but even if we suppose that 6.36 is an overestimate we find (with 95% probability) that the true value is unlikely to be lower than 4.6 months (Fisher and Yates' table of variance ratios[14]).

If an observer who had a standard deviation of 4.6 months, and a mean systematic error of −2 months, assessed an individual film, he could estimate his possible difference from the expert assessment by using twice the standard deviation, thus: $-2 \pm 2 \times 4.6$; i.e., from −11.2 to +7.2 months. That is to say, his assessment might be nearly 12 months too low or more than six months too high, as compared with an expert's assessment. Such a degree of uncertainty, if found common among observers, would cast serious doubt on the general usefulness of the assessment method for individual RGs.

Possible Causes of High Variation in Systematic Error: It might be suggested that RBM's high variability reflects the erratic nature of her assessments. But this explanation seems unlikely, because in any kind of measurement if an observer is erratic the effect appears as a large variable or random error, represented in skeletal assessment by variation between readings of the same RG, without reference to systematic error at all. In RBM this intrafilm variation was relatively small. Indeed, it was estimated (by an analysis of components of variance) that even if there had been no difference whatever between repeated readings of the same film, the standard deviation 6.36 would have been reduced by only a half a month, to 5.85 months.

Therefore four other possible causes of the great variation in systematic error were considered:

1. RBM's assessments were done on RGs reproduced on paper. Although no relationship between quality of RG and size of error was detected, all the pictures were more difficult to assess than are actual films.

2. The range of variation has been estimated by factors derived from the normal curve, whereas the frequency distribution of systematic errors may differ from that curve. This possibility could not be tested on this data, but inspection suggested that the variation might be smaller than the normal curve estimate had indicated. If a test series contained 100 RGs this factor could be explored.

3. The expert assessment on each film has been used as if it would not change when the same expert made another independent assessment of the same film. This is unlikely and therefore part of the variation in RBM's systematic error presumably represents simply the amount by which an expert would differ from himself in reassessment.

4. The main cause for the large variation in systematic error may be the factor already suggested, namely, the lack of independence of expert assessments.

Numbers of Roentgenograms Required for Estimating Variation: The following figures illustrate the effect of increasing the numbers of RGs in estimating the standard deviation of the systematic error for individual films (Fisher and Yates' table of variance ratios[14]):

1. Having estimated the standard deviation from 50 films an author could state with 95% probability that, if the true standard deviation were higher than his estimate (S.D.), it would not be greater than S.D. + 20% of S.D.

2. With 100 RGs the factor would be about 13%.

3. To reduce the factor to 10% would require about 150 RGs.

Error in Estimation of a Child's Progress

The estimate of a child's progress during six months or a year is usually much more

valuable than the estimate of his status at any one time; but here again the observer should know what allowance to make for his systematic error. From each of the 10 children the first pair and the last pair of RGs were used, as illustrated here by the data from Betty. (Units are months. For RBM the means of duplicate readings on each film were employed.)

Pair of Films	Chronologic Increase	Increase in Skeletal Age			
		RBM's Assessments		Experts' Assessments	
		Todd's Atlas	G.-P. Atlas	Todd	GP
First	2	6.5	7.5	5	4
Last	14	12.0	15.0	10	16

When the chronologic increase was small, e.g., 2 months, RBM's assessed "increase" was sometimes negative, e.g., −1.5 months. This is bound to happen when all assessments are made independently, and would be reported for clinical purposes as "No progress detected," but the actual assessment would remain on record. It is perhaps noteworthy that none of the expert assessments produced such negative differences.

Analysis of the data from all 10 children showed no significant differences among the four estimates of progress—RBM with Todd's atlas, RBM with the Greulich-Pyle atlas, Todd and GP. The mean differences between RBM's estimate of progress and those of the experts were: RBM − GP = +0.30 month; RBM − T = −0.10 month. These averages were far from significant, but the variation in the 20 estimates of the RBM − GP difference (2 estimates from each child) was great. It was expressed by a standard deviation of 4.7 months, which was essentially the same as the estimate, 4.6 months, for the RBM − T comparison (2 randomly selected RGs from each of 15 children). These estimates were confirmed by the value, 5.1 months, obtained by using all the information on the variability of RBM's systematic error among RGs of the 10 children on whom the GP comparison was made.

Even if, on the average, an observer does not differ from an expert in the estimation of children's progress, with a standard deviation of such magnitude he cannot place much reliance on his estimate of an individual's progress. Thus, the usual estimation of twice the standard deviation would indicate a possible difference from the expert of ± 10 months. Much of this variation is due to the variation in systematic error between RGs from the same child, and it might be much lower on a properly prepared series of test films.

Comparison of Experts and Atlases

The Macy data make it possible to compare with each other not only the "T" and "GP" assessments already used, but also other assessments by Pyle on the same films as she had

TABLE 3

Expert Assessments of Skeletal Age from Hand RGs of Phyllis

Chronologic Age (mo.)	Skeletal Age (mo.)		
	Todd	Greulich-Pyle	Todd (1950)
73	82	73	73
75	86	77	76
83	95	86	86
97	101	103	102

assessed to give the GP series. These other assessments, indicated as "T(1950)," were made with the Greulich-Pyle atlas (published in 1950), but by Todd's method, which places emphasis on the more advanced centers. Ten children provided films for this three-fold comparison, which is exemplified in table 3.

Differences between Atlases and Methods: As in the first analysis of RBM's data, the figures for each child were analyzed separately, and then the probabilities were combined. The results were as follows:

1. The original Todd assessments showed a significant tendency to be higher than the GP assessments (P less than 0.01), but the 63 individual RGs showed that the GP assessments might be 14 months lower or 10 months higher than the Todd assessment of the same films.

2. The original Todd assessments showed a significant tendency to be higher than the T(1950) assessments, i.e., Pyle's assessment with the Greulich-Pyle atlas but by Todd's method (P less than 0.01).

3. There was no consistent tendency for the T(1950) assessments to be higher or lower than the GP assessments. None of the 10 mean differences was significant, and the combined probability was approximately 0.5.

It may be concluded, therefore, that the difference between the original Todd assessments and the Greulich-Pyle assessments is due rather to the change in the atlas standards than to the change in the method of assessment.

Differences between Children: The data were next arranged as follows:

Child	Differences (T − GP) in months
Billy	+2, +3, −7, +4. Mean = +0.50
Bobby	−1, −1, −4, +3, −4, 0. Mean = −1.17

etc.; and likewise for the differences T − T(1950) and T(1950) − GP.

The most striking fact emerging from this analysis was that the mean differences varied significantly between children (P less than 0.001); and this was true in all three sets of comparisons, even in the T(1950) − GP series where, as stated above, there was on the average no significant difference between the two assessments.

This is the same peculiarity as was found in comparing RBM with GP and with T; and it seems to strengthen the suggested explanation, for it could arise if the assessments by any one observer were influenced by the same observer's assessments on other RGs from the same child or by other knowledge of the child. In this comparison of atlases there is, of course, another possible explanation, namely, that the atlas standards at certain ages have been changed more than at other ages, and that therefore children of different ages were unequally affected by the revision. Inspection of the individual assessments, however, did not support this explanation.

Estimates of Children's Progress: As in the study of RBM's variation in the assessment of progress, the children provided 10 first pairs of RGs and 10 last pairs. In both sets of pairs the mean differences between estimates of progress, T − GP, were small and non-significant (+0.5 month in the first pairs, −0.4 month in the last pairs). The individual differences, however, were large. In the 10 first pairs they ranged from −6 to +3 months, in the 10 last pairs from −11 to +11 months. Thus, one child (Billy) with RGs taken 26 months apart was assessed as having gained 40 months in skeletal age (T) and 29 months (GP). Another child (Phyllis) with RGs 14 months apart was assessed as having gained 6 months (T) and 17 months (GP). In these instances the GP assessment of

progress was nearer the chronologic increase than was the T assessment, but often the reverse was true.

The general conclusion from this comparison of experts and atlases is that even expert assessment of skeletal maturation has not yet reached a desirable degree of stability.

Requirements for a Set of Test Roentgenograms

The provision of even the simplest method whereby observers could make unbiased estimates of their errors of assessment would be preferable to the present state of ignorance. Such provision could be made as follows.

The expert should make a strictly random selection of RGs (one per child) from his collection, or, much better, from another collection, in order to avoid previous knowledge of the films or other data regarding the children. No collection would reproduce exactly the features of the various observers' own series of RGs, but if the collection used for sampling were very variable in age, condition of maturation and state of health of the children, the results would be as nearly suitable for observers in general as could be expected from a simple scheme.

Sample sizes have already been discussed.

The expert should assess the RGs in random order, knowing only the sex of the children. The observer who tests himself should also assess in random order and in the same state of ignorance. He should see the expert's assessments only after finishing all his own, including his second reading if he makes two.

In preparing the set of RGs the expert could investigate several important questions, with the aid of observers who would try the test series before it was distributed widely. Such an investigation should be carefully planned to permit proper analysis of the results, and it could include the following three items:

1. Variable error, estimated from duplicate readings, a month or more apart.
2. Variation of systematic error with age of child. Roentgenograms could be grouped by age, and if it was found that such variation was large the final test series should be arranged likewise. (The actual regression relationship would, it is suspected, be nonlinear, and too complicated for general use.)
3. Differences in systematic error between RGs of the same child. If such differences were found, at least two films from each child would be needed in the test series.

An Experiment for the Reader

Wide distribution of expertly assessed RGs may be considered too expensive, but the comparison of any two observers, which may be equally important, need cost little or nothing, and a procedure like the one just outlined would be appropriate. The reader may be interested in performing a small-scale experiment of this kind by comparing his assessments of the Macy RGs with those made by RBM using the Greulich-Pyle atlas. Therefore her values are stated here for 20 randomly selected RGs serially numbered for each child in the order in which the RGs occur in the book (one RG per child).

The book should be prepared in advance by another person, as described under Methods. Each of the 20 pictures should be assigned a letter or number, and only the sex of the child should be indicated. The children are not in alphabetical order in the book, and so the following list should provide no clues. The data are: name, serial number of RG in parenthesis, RBM's first and second readings in months.

Barbara(7): 192, 192.
Bobby(2): 71, 65.
Donald(3): 75, 72.
Jean(1): 62, 67.
Judy(1): 41, 42.
Norman(1): 51, 49.
Robert(2): 66, 70.
Betty(5): 90, 92.
Calvin(1): 136, 137.
Frank(7): 158, 159.
Jimmy(5): 79, 76.
Mae(1): 38, 37.
Paul(1): 76, 80.
Shirley(2): 81, 82.
Billy(4): 127, 132.
Charldine(2): 68, 67.
Herbert(1): 67, 63.
Josephine(1): 84, 80.
Maynard(2): 45, 46.
Phyllis(1): 77, 76.

If the reader makes only one reading he can take the first of each pair of readings in the above list. If he makes two readings about a month apart and finds their means, he should use the means of the above pairs for comparison.

The differences could be expressed as "Reader—RBM," and the mean of the 20 differences could be tested for significance by Fisher's *t*.

By referring to Macy (vol. 3, pp. 2110-2118) the reader could compare his assessments on 10 of the RGs with those of Pyle using the Greulich-Pyle atlas.

An Appeal for Data

Any reader who performs the above experiment could make a useful contribution to a survey of errors in skeletal assessment by sending his or her data to the authors at the New York University College of Medicine, 477 First Avenue, New York 16, N.Y.; such contributions would be greatly appreciated. The most useful form of the data would be:

1. A statement for each of the 20 RGs showing not only the average but the assessment on each indicator (each carpal, epiphysis, etc.) individually.

2. A second reading made one month after the first, in a different random order from the first series, and without knowledge of the previous reading. (The chronologic age and the assessments made by Todd, Pyle and RBM should not be ascertained until after the second reading.)

If, however, the above information should appear too elaborate, a single reading of each picture, without separate statements for each indicator, would provide useful data.

Only the raw data without statistical tests are desired, along with brief statements regarding: (1) the sequence in which the RGs were assessed; (2) the observer's experience in assessing (e.g., source of instruction, duration of experience and approximate number of RGs assessed already); (3) previous experience, if any, with the Macy RGs.

To avoid biased selection of results it is important that the decision whether to send the data or not be made before the assessing is started, and that the decision be adhered to, regardless of the good or bad appearance of the results. (The authors would appreciate receiving a postcard announcing such a decision.)

For those who are unfamiliar with tables of random numbers (Fisher and Yates,[14] or extracts from Kendall and Smith, reproduced by Arkin and Colton[15]) the authors will be glad to supply the random sequences for assessments, with other information that might be requested regarding the experiment. In any report on data sent there would, of course, be no identification of observers with particular results.

Summary

Because of the increasing use of skeletal maturation in the study of children's development and health, thorough exploration of the systematic and variable errors of skeletal age assessment is desirable. The systematic error of one observer (RBM) has been studied by comparing her assessments of hand RGs, reproduced in Macy's *Nutrition and Chemical*

Growth in Childhood, with the published assessments of the same RGs by experts using the same atlases—Todd and co-workers using Todd's atlas and Pyle using the Greulich-Pyle atlas.

RBM's assessments, including duplicate readings on each RG, were all independent of each other, i.e., made without knowledge of chronologic age, of other assessments of the same RG or other RGs from the same child, or of any other information about the child except sex.

RBM tended to estimate the skeletal ages lower than did the experts, and this tendency was greater in the Greulich-Pyle comparison than in the Todd comparison. Her systematic error varied significantly between children and between RGs of the same child. It is suggested that these variations may have arisen from the experts' assessments not being strictly independent.

Even if other observers had as large and as variable a systematic error as RBM, the skeletal assessment method would probably be sufficiently reliable in the comparison of average skeletal ages of groups of children, but it would be of doubtful value in the assessment of a single RG or of a child's progress.

Comparison of the expert assessments with each other showed that the change of the atlas (from Todd to Greulich-Pyle) has altered greatly some of the estimates of skeletal ages in the Macy RGs and even expert assessment has not yet reached a desirable degree of stability.

The requirements in the preparation of a series of test RGs by an expert are outlined. An experiment is described which the reader can conduct on the Macy RGs, and an appeal is issued for the contribution of the data from such experiments to a survey of errors in skeletal assessment.

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SPANISH ABSTRACT

Valoración del Método de Medir la Edad Osea para Estimar el Desarrollo de los Niños

I. Errores Sistemáticos en la Apreciación de las Radiografías

La valorización y apreciación del desarrollo y estado de salud de los niños con los atlas radiográficos sobre maduración esquelética, especialmente el atlas de la mano de Todd y su sucesor el atlas de Greulich-Pyle, se aplica más amplia y frecuentemente; por ejemplo, en estudios sobre nutrición, en exámenes físicos en la infancia, para control terapéutico endócrino y para predecir la estatura adulta de un niño. Al compararse la radiografía de la mano de un niño y la de un atlas, se estima la edad ósea del niño; cuando no concuerdan las diversas partes (carpianos, epífisis y vainas) de la radiografía en estudio con la radiografía standard del atlas, se acepta generalmente como la edad esquelética de la mano, la media de las edades óseas del conjunto de partes. Sin embargo, poca atención se ha dado a los errores de observación en estas apreciaciones, lo que ha ido creando problemas de importancia; quienes emplean el método no son sólo quienes hayan estado en contacto con Todd y sus colaboradores o sus sucesores; quien hace la apreciación puede ser cualquier médico que tenga una copia del atlas, ye sea pediatra, endocrinólogo o nutriólogo.

Recientemente se han encontrado serios grados de error en las pruebas y técnicas comunes en hematología, química clínica y diagnóstico radiológico torácico; como la valorización esquelética es un método relativamente nuevo, los autores creyeron prudente analizar causas de error aun cuando los resultados que obtengan ganen la duda para su propia habilidad y capacidad de observación.

Dos tipos de error deben analizarse en todo método de observación: el sistemático y el variable.

El error sistemático en la apreciación del desarrollo óseo lo definen los autores como la diferencia persistente entre la apreciación del observador y la apreciación de la misma radiografía por un experto. El error variable lo determinan las diferencias encontradas por el mismo observador con observaciones independientes utilizando el mismo atlas con las mismas radiografías, cuando las valoraciones repetidas no muestran tendencia sostenida a aumentar o disminuir.

En este artículo los autores tratan únicamente de analizar el primer error o sea, el error sistemático, con tres fines definidos:

1. Comparar las observaciones de uno de ellos, a pesar de su falta de experiencia, con las de los expertos y otros observadores, y estimar su error sistemático.
2. Investigar las causas posibles del error sistemático.
3. Comparar entre sí, las apreciaciones de diferentes expertos.

El error sistemático de uno de los autores (R.B.M.) se estudió comparando sus apreciaciones sobre las radiografías de mano del libro de Macy sobre "Nutrición y Crecimiento Químico en la Infancia," con las apreciaciones de expertos sobre las mismas radiografías, usando los mismos atlas (Todd y colaboradores usando el atlas de Todd, y Pyle usando el atlas de Greulich-Pyle).

Las apreciaciones de R.B.M. fueron todas independientes entre sí, aún las realizadas por duplicado con una misma radiografía; las hizo sin conocer la edad cronológica, las lecturas previas de la misma radiografía o de otras radiografías del mismo niño ni ninguna información sobre ese niño excepto el sexo. R.B.M. tendió siempre a estimar edades óseas inferiores a las señaladas por los expertos, tendencia que se acentuó con el método de Greulich-Pyle en comparación con el de Todd. Su error sistemático varió significativamente entre niños y entre radiografías del mismo niño, por lo que se pensó que estas variaciones pueden deberse al hecho de que las observaciones de los expertos no fueron estrictamente independientes. Aún aceptando que otros observadores tuvieran error sistemático tan grande y tan variable como el de R.B.M., los autores consideran digno de confianza el método esquelético para comparar las edades óseas promedio de grupos de niños pero de valor dudoso en la valoración de una sola radiografía o del progreso de un niño.

La comparación de las apreciaciones entre los expertos muestra grandes alteraciones en las estimaciones de las edades óseas en las radiografías de Macy, cuando usaban el atlas de Todd o el de Greulich-Pyle; por lo que los autores aceptan que no se ha alcanzado estabilidad aún ni siquiera entre las apreciaciones de los mismos expertos.

En vista de estos hallazgos, los autores sugieren algunos requisitos para realizar una serie de pruebas de lectura de radiografías y describen una prueba personal para que el lector las realice con las radiografía de Macy, haciendo un llamado a todos los que la practiquen para informarles sus lecturas y estudios a fin de analizar los errores en las apreciaciones óseas.

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ENDOCARDIAL FIBROELASTOSIS

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THE characteristic clinical features of endocardial fibroelastosis are paroxysmal dyspnea, cyanosis and cardiomegaly. Because these manifestations frequently are terminal the premortem diagnosis seldom has been made. However, it is now apparent that affected infants sometimes survive for long periods and recognition of the disease is possible.[1] The purpose of this report is to introduce a classification of the clinical patterns

TABLE 1

SOURCES OF 149 CASES OF ENDOCARDIAL FIBROELASTOSIS PROVED AT AUTOPSY

Authors	No. of Cases	Authors	No. of Cases
Adams and Katz[1]	17*	Lippincott[19]	1
Benjamin and Simon[2]	1	MacGregor and McKendry[20]	1
Blumberg and Lyon[3]	23†	Mahon[21]	2
Bocian and Defoe[4]	1	Neely[22]	3
Collier and Rosahn[5]	2	Powers and Le Compte[23]	1
Cosgrove and Kaump[6]	49	Prec and Cassels[24]	1
Dennis et al.[7]	1	Prior and Wyatt[25]	8
Edmonds and Seelye[8]	6	Rossman[26]	1
Engel and Lynxwiler[9]	1	Rotem[27]	1
Glynn and Reinhold[10]	1	Sano and Anderson[28]	1
Gross[11]	1	Schefrin[29]	1
Hill and Reilly[12]	1	Sprague[30]	1
Katzenstein[13]	3	Stadler et al.[31]	1
Kenny and Sanes[14]	2	Weinberg and Himelfarb[32]	2
Kugel[15]	1	Weisenfeld and Grayzel[33]	1
Leary et al.[16]	1	Weisman[34]	2
Letteer[17]	2	Wulliamy[35]	2
Lewis[18]	3	Other sources: Cabot Case[36] Records, Massachusetts General Hopsital	4

* Twenty-one reported but 4 still living.

† Twenty-five reported but 2 were cases with infantile coarctation of aorta.

of endocardial fibroelastosis and to demonstrate its use in the consideration of the differential diagnosis.

The data presented have been obtained from a review of the clinical and necropsy findings in 149 infants and children proved to have the disease. The number of cases reported by the various authors is listed in table 1.

CLINICAL TYPES

From the age incidence, type of onset, symptomatology and course of illness it is possible to identify three distinct types of clinical picture in endocardial fibroelastosis. These have been designated fulminating, acute and chronic types.

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The fulminating type of disease occurred in 25%. The infants usually were under 6 weeks of age and had been considered normal before an abrupt onset of dyspnea with cyanosis. Survival after onset was only a matter of minutes, or hours, and an occasional crib death was reported. In a rare instance the infant was cyanotic and in cardiac failure at birth. In general, the younger the infant the shorter the course.

The acute type made up 51% of the total and was seen in infants between 6 weeks and 6 months of age. They had been considered to be in good health prior to an unexpected paroxysm of dyspnea with cyanosis, the initial attack sometimes being ascribed to aspiration or choking. Repeated paroxysms followed and between attacks irritability, anorexia, tachycardia and spasmodic coughing became increasingly apparent. A globular type of cardiomegaly was found on roentgenographic examination. The symptoms culminated in fetal syncope characterized by shock, respiratory distress and cyanosis not relieved by oxygen. Survival after the onset was less than four weeks and averaged only 15 days.

The chronic type occurred in the remaining 24%. Usually involved were older infants and children but, at times, symptoms were noted during the first 6 months of life. The characteristic onset was slow with anorexia, irritability and decreased rate of growth in a previously well child. A spasmodic hacking cough, presumed to represent respiratory disease, usually appeared at some time during the illness. Chest roentgenograms nearly always revealed cardiomegaly and served to introduce heart disease as a diagnostic consideration. Dyspnea and cyanosis were not conspicuous until the terminal phase and digitalis sometimes seemed to produce a remission. When death did occur, after a few months or years, it was often unexpected with sudden dyspnea, cyanosis and shock typical of the acute disease.

Although the age of onset was earlier than usual, the characteristic progression of symptoms in this type is illustrated by the case citation of an infant on the authors' service.

Case Report

P.G., a white male infant, had been considered normal until the age of 12 wk. when anorexia and irritability developed. About 1 wk. later a hacking cough appeared and was ignored until it

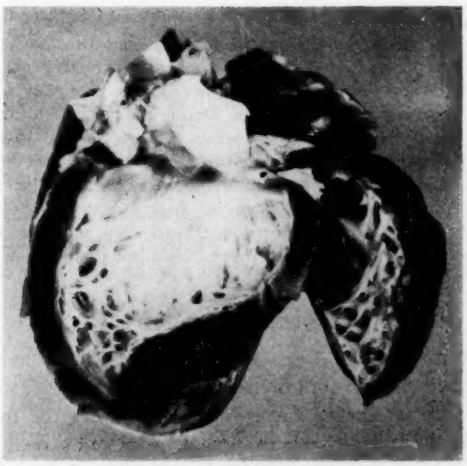

Fig. 1. Dilated and hypertrophied left ventricle with thick, white, opaque endocardium in 5½ mo. old infant (P.G.)

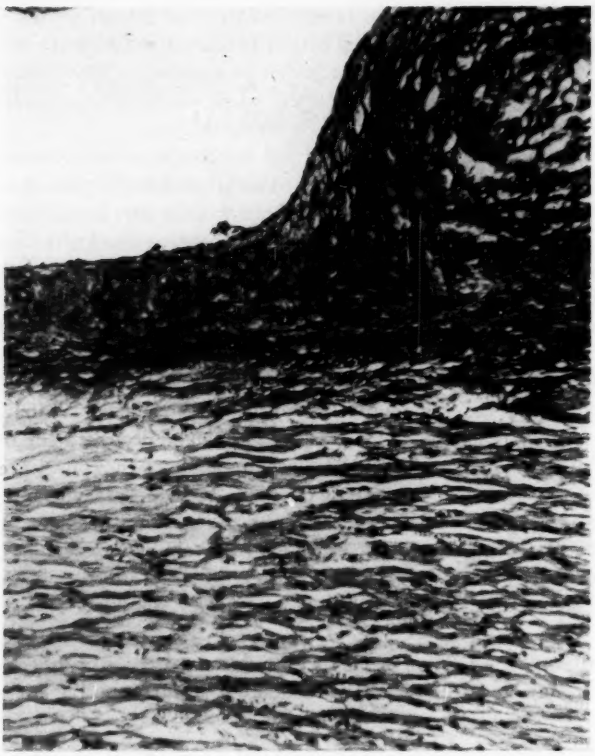

FIG. 2. Marked fibroelastic thickening of left ventricular endocardium in Patient P.G. (Verhoeff-Van Gieson elastic tissue strain) × 150

became paroxysmal in nature. The possibility of pertussis was considered but not confirmed. Laboratory findings were inconclusive. Chest RGs showed increased vascular markings but heart size was within normal limits. Moist rales were heard in both lung fields and an expiratory wheeze was present. The heart was normal on percussion and auscultation. During the next 6 wk. the respiratory symptoms improved but did not disappear. There was no weight gain. At 5½ mo. of age the infant suddenly appeared to choke and there was a short period of dyspnea and cyanosis. Several hours later a similar attack compelled a hurried trip to the hospital but the baby was dead on arrival. At autopsy the heart weighed 75 gm. (expected 30 gm.). There was marked hypertrophy of the left ventricle. The endocardium of the left side of the heart was opaque, pearl white and thickened. Valve leaflets were normal. Verhoeff's special elastic tissue stain showed abundant proliferation of elastic tissue fibrils in the endocardium. (See Figs. 1 and 2.)

PHYSICAL FINDINGS

Infants who died after a short illness were in a good state of nutrition. On the other hand, infants and children with the chronic type showed evidence of impaired nutrition and retarded development. During the episodes of dyspnea the infants were anxious, unresponsive, displayed respiratory embarrassment, shock and varying degrees of cyanosis. Costal and sternal retraction were prominent signs in young infants. Bubbling rales were heard bilaterally during paroxysms but were replaced by expiratory wheezes on recovery.

TABLE 2

SIGNS AND SYMPTOMS IN 149 INFANTS AND CHILDREN WITH ENDOCARDIAL FIBROELASTOSIS

Signs and Symptoms		No. of Patients
Respiratory difficulty		133
* dyspnea	107	
tachypnea	5	
rapid and shallow breathing	4	
crowing and grunting	4	
expiratory wheeze	34	
orthopnea	4	
Cyanosis with attacks of dyspnea		106
Cough, with or without evidence of respiratory infection		62
Anorexia and failure to gain weight		54
Irritability		44
Vomiting		39
Right heart failure (edema, hepatomegaly)†		22
Precordial murmurs		31
Malaise or weakness		12

* Descriptive terms used by authors.

† Right heart failure was late symptom and followed left heart failure.

Cardiomegaly was almost never noted on physical examination. Tachycardia was commonly observed. Precordial murmurs were present in only 30 subjects (20%). Clubbing of the digits was not observed. Cyanosis was usually a terminal feature but was not invariably present in the early attacks of dyspnea. Fever was present only with concurrent infection. The symptoms and signs described are summarized in table 2.

LABORATORY FINDINGS

Routine laboratory studies were consistently noncontributory. Hemoglobin and red blood cell counts were all within normal limits except for an occasional secondary anemia. Leukocytosis was noted only in the presence of coincidental infection. Glucose tolerance tests in three patients were normal. Nasopharyngeal swabs were unrevealing and blood cultures were negative.

Roentgen examination of the chest was made in 74 instances and in 63 (85%), there was cardiomegaly of a globular or diffuse type.

Electrocardiographic tracings were made on 39 subjects and in every instance were considered to be abnormal; however, no consistent nor characteristic pattern was discernible. The most common deviation was depression of the T-waves, a not unusual finding when there is myocardial ischemia from any cause. However, definite inversion of the T-wave was observed in only one lead of a single patient. (See table 3.)

GENERAL FEATURES

It is not possible to determine the exact incidence of this disease in the childhood population. Katzenstein[13] reported three cases within one year among 20 autopsies on infants; Collier and Rosahn[5] reported two cases in 205 autopsies on infants; and Blumberg and Lyon[3] stated that in their experience the condition was one of the common causes of sudden death in infants. Difference in sex incidence is not striking, with 75 males and 66 females listed. As regards race, the proportion of white to Negro patients was approxi-

TABLE 3

ELECTROCARDIOGRAPHIC CHANGES REPORTED IN 39 SUBJECTS WITH ENDOCARDIAL FIBROELASTOSIS

Abnormality		No. of Cases
Abnormality in T-waves		12
Depressed T_1	4	
Diphasic T_1, T_2, T_3	2	
Inverted T_2	1	
Flat T_2, T_3	1	
Low T_1, T_2	1	
Low T_1, T_2, T_3	1	
S-T_1 elevated and S-T_3 depressed	1	
Sinus tachycardia		7
Prolonged QRS		4
Prolonged Q-T		2
Notched or peaked P		2
Biphasic QRS		1
Prolonged P-R		1
"Heart block"		3
"Abnormal tracing"		7

TABLE 4

AGE AT TIME OF DEATH IN 149 SUBJECTS WITH ENDOCARDIAL FIBROELASTOSIS

Age at Death	No. of Cases
Stillborn	2
1 day to 2 mo.	42
2 to 6 mo.	42
6 to 12 mo.	27
1 to 3 yr.	22
3 to 6½ yr.	7
11½ yr.	1
Unknown	6

TABLE 5

CONDITION OF VALVES IN 149 CASES OF ENDOCARDIAL FIBROELASTOSIS

Description of Valves	No. of Cases
Aortic stenosis or atresia	18
Aortic and mitral stenosis	28
Aortic and tricuspid stenosis	1
Mitral stenosis or atresia	10
Mitral and tricuspid stenosis	3
Mitral insufficiency	2
Pulmonic and tricuspid stenosis	2
Tricuspid stenosis	1
All valves stenosed	3
Normal	63
No description given	18

mately that of the general population. Data concerning the age at death are recorded in table 4.

Pathologic Aspects

Gross findings revealed cardiac enlargement in 94% of the 119 cases in which heart size was given. Consistently, the endocardium was thickened, opaque and gray or pearl white. The left ventricle was involved in 98% of the 131 cases where location was specified. The process was limited to the left side of the heart in 82%. There were valvular deformities in 68 (51%) of the 131 cases in which the valves were described. The aortic and mitral valves were involved most frequently. (See table 5.)

Microscopic studies disclosed hyperplasia of the fibrous and elastic tissue components of the endocardium. The elastic process frequently projected a short way into the myocardium. Calcifications were common in the endocardium, myocardium and especially the papillary muscles. Vacuolization and apparent degeneration were sometimes seen in the myocardium. There was never leukocytic infiltration, Aschoff nodule formation, nor findings of an inflammatory lesion. The hyperplasia was most marked in the cases with valvular deformity but the valves were not always directly involved by the process.

Differential Diagnosis

To be considered in the differential diagnosis are conditions often referred to as idiopathic cardiomegaly and include coarctation of the aorta (infantile type), anomalous left coronary artery, beri-beri, rhabdomyoma, and the cardiac type of glycogen storage disease. Elucidation of the diagnosis by use of the clinical classification of endocardial fibroelastosis is outlined as follows (see table 6):

A. Fulminating Type: Whenever cardiac failure is present at birth, or in the case of sudden death in infancy, this type of fibroelastosis must be considered. The short course of illness seldom allows for premortem diagnosis.

B. Acute Type: Because sudden dyspnea and cyanosis in infants 6 weeks to 6 months of age are characteristic features, the acute type is the one most likely to be confused with other conditions associated with cardiomegaly. Distinguishing features of each assist in making the diagnosis of endocardial fibroelastosis by exclusion.

1. Coarctation of the aorta is characterized by an absent femoral pulse and relatively low blood pressure in the legs. In the infantile type the coarctation is proximal to a patent ductus arteriosus and it sometimes is possible that venous blood will be shunted into the aorta and produce femoral pulsation. Even so, blood pressure in the legs remain relatively low. Theoretically, cyanosis may be more intense in the feet than in the hands and face, but case reports indicate this usually does not occur.

2. Anomalous left coronary artery (from the pulmonary artery) produces definite inversion of the T-waves in the ECG. (In fibroelastosis T-waves frequently are of low amplitude, or flattened, but almost never inverted.) Until late in the course of the disease apparent pain on effort, dusky pallor and profuse sweating are more prominent symptoms than are dyspnea and cyanosis. The infant is usually described as a poor feeder.

3. Beri-beri heart rarely occurs in this country. It is apt to be found in the breast-fed infant of a malnourished mother. Ptosis of the eyelids, loss of reflexes, and other neurologic signs may be present. The cardiac enlargement may be predominantly right sided, accompanied by hepatomegaly and peripheral edema. Response to thiamine therapy is diagnostic.

4. Rhabdomyoma, a congenital nodular tumor of the heart, rarely causes symptoms

TABLE 6

DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC CARDIOMEGALY

	Endocardial Fibroelastosis			Coarctation of Aorta (infantile)	Anomalous Left Coronary Artery	Beri-beri Heart	Rhabdomyoma	Glycogen Storage Disease (cardiac)
	Fulminating Type	Acute Type	Chronic Type					
Age	Under 6 wk.	1 to 6 mo.	½ to 11½ yr.	1 to 6 mo.	1 to 6 mo.	Infancy	Any age	Infancy
Abrupt onset with dyspnea and cyanosis	Yes	Yes	No	Yes	Sometimes	No	Usually	No
Nutrition at onset	Good	Good	Good (later poor)	Usually good	May be good	Poor	Good	Usually not good
Femoral pulse	Normal	Normal	Normal	Diminished or absent	Normal	Normal	Normal	Normal
Characteristic ECG	No	No	No	No	Usually inversion of T-waves	No	No	No
Miscellaneous features	Sudden death common	Death within 4 wk. of onset	Respiratory disease suspected	B.P. low in legs. Cyanosis in feet may be marked	Apparent pain with activity, pallor. Poor feeder.	Neurologic signs. Response to thiamine.	Signs of tuberous sclerosis (café au lait spots, convulsions, mental retardation)	Increased glycogen in skeletal muscles common.

unless situated on the valve leaflets. According to Batchelor et al.[37] the most constant clinical feature is sudden death after a minor illness. Rhabdomyoma, in more than 50% of the cases, has been accompanied by tuberous sclerosis with mental retardation, convulsions, sebaceous adenoma, and café-au-lait spots.

5. Glycogen storage disease (cardiac type) may present abnormal glycogen deposition in the skeletal muscle as well as in the heart muscle.[38] Hence, a useful diagnostic test would be tissue analysis after skeletal muscle biopsy. The cardiac type is not characterized by the hypoglycemia, ketosis and negative response to adrenalin administration seen in true von Gierke's disease.

C. Chronic Type: Because of the older age group, slow onset, and prolonged course of this disorder, it is unlikely that the aforementioned conditions will be confused diagnostically with chronic endocardial fibroelastosis. Demonstration of cardiomegaly and the presence of respiratory symptoms, without respiratory disease, constitute presumptive evidence of the chronic type of this condition.

Discussion

The altered physiology in endocardial fibroelastosis is that of left heart failure with acute pulmonary edema. The pathogenesis has not been established. According to Rauchfuss,[39] it was Kreysig who first (1816) designated this type of lesion as fetal endocarditis. For more than a century, intrauterine infection was thought to be responsible and as late as 1933, Farber and Hubbard[40] discussed maternal infection as a possible cause. Campbell,[41] however, observed that rubella was the only maternal infection of proved etiologic significance in congenital heart disease; no instance of rubella was found in the prenatal history of the subjects with endocardial fibroelastosis. Potter[42] states that it is not logical to assume that a fetal infection could produce such a severe localized lesion. Hill and Reilly[12] suggested this condition might represent a collagen disease because of the presence of fibrinoid degeneration in their case. Fibrinoid degeneration is not pathognomonic of collagen disease[43–45] and, furthermore, has not been reported in fibroelastosis by other authors.

Gross[11] in 1941 clearly defined the entity endocardial fibroelastosis. Collier and Rosahn[5] thought the condition might represent altered genetic constitution, but they did not dismiss the possible effect of environmental factors. Reports of three sets of twins,[25, 46, 47] only one of each set having endocardial fibroelastosis, and the report by Weinberg and Himelfarb[32] of the anomaly in siblings appear to support a concept of developmental defect.

The fate of the bulbus cordis in the human heart may be pertinent to the pathogenesis of fibroelastosis of the endocardium.[8] Sir Arthur Keith[48] demonstrated the bulbus cordis to incorporate into the ventricles early in embryonic life and the bulbus, like the ventricles, divides into right and left parts. The right bulbus persists as a part of the right ventricle and infundibulum but the left bulbus normally atrophies and disappears. Impressed by the unusual character of the developing endocardial tissue in the primitive bulbus, Keith stated, "It is endowed with most remarkable formative qualities. It behaves in the developing heart exactly as does the granulation tissue of a healing wound." This suggests to us that left-sided endocardial fibroelastosis results when there is persistence and overgrowth of the proliferating endocardium of the left bulbus cordis. Organization and contraction of this "granulation-like" tissue could produce a thickened fibrous endocardium, distort the valves, impair left ventricle output, and obstruct thebesian vessels to produce myocardial ischemia. On such a basis there is plausible explanation for the site and character of the lesion. Occasional occurrence in the right heart could follow overgrowth of the lining of the right bulbus.

Fibroelastosis of the endocardium of the left ventricle accompanies cases of infantile coarctation of the aorta[49] and of anomalous left coronary artery.[50] The possibility of etiopathologic relationships between these conditions and endocardial fibroelastosis exists.

Summary

Based on the study of 149 case reports it appears that endocardial fibroelastosis is an entity which manifests itself in three distinctive types of clinical pattern. These have been designated fulminating, acute and chronic types of disease, according to the age group, type of onset, symptomatology and course of illness. Utilization of this clinical classification to make the differential diagnosis of idiopathic cardiomegaly is described. Pathologic findings are summarized and tabulated. Pathogenesis is speculative but developmental defect resulting from persistence and overgrowth of the primitive lining of the left bulbus cordis best explains the site and character of the lesion.

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SPANISH ABSTRACT

Fibroelastosis Endocárdica

Las características clínicas de este padecimiento son disnea paroxística, cianosis y cardiomegalia. Pocas veces se ha hecho el diagnóstico antes de la muerte, pero como los enfermos pueden vivir por muchos años, el diagnóstico oportuno es posible.

Tomando en consideración la edad, la forma de iniciación y la evolución de los síntomas y del padecimiento en sí, los autores lo clasifican con tres formas clínicas: la aguda fulminante, la aguda y la crónica.

La forma aguda fulminante se presentó en el 25% de los casos y en niños menores de seis meses de edad. Después de un cuadro brusco de disnea y cianosis en un niño aparentemente sano, la muerte se presentó en cuestión de minutos u horas. En otros casos los niños presentaron desde el nacimiento trastornos cardiacos y la muerte se consideró accidente de cuna.

La forma aguda se presentó en el 51% de los casos, en niños de seis semanas a seis meses de edad. Generalmente un niño de aspecto normal presentaba accesos bruscos de disnea paroxística y cianosis; en los intervalos de los accesos el niño se veía irritable, anoréxico y con crisis de tos espasmódica. La evolución era siempre fatal con un promedio de sobrevivencia de 15 días.

La forma crónica se presentó en el 24% restante, en niños de seis meses a 11 años de edad. El principio simulaba un trastorno respiratorio acompañado de anorexia e irritabilidad; las radiografías de tórax mostraron casi siempre cardiomegalia de tipo difuso y globoso, considerada como idiopática. La disnea y la cianosis aparecían tardíamente, y la muerte meses o años después del principio.

En los 149 casos estudiados, los hallazgos patólogicos consistieron en cardiomegalia (94%), engrosamiento hiperplásico del endocardio del corazón izquierdo (98%) y anormalidades valvulares (51%). Invariablemente hubo insuficiencia cardiaca izquierda acompañada de edema pulmonar agudo. Se observó crecimiento cardiaco en el 85% de los 74 casos estudiados radiológicamente. El electrocardiograma tomado en 39 pacientes fué anormal sin ninguna modalidad característica. Los demás datos del laboratorio no fueron de utilidad clínica.

La patogenia no se ha explicado.

El diagnóstico diferencial debe hacerse con todos aquellos trastornos que producen cardiomegalia, como, por ejemplo, coartación de la aorta, presencia de arteria coronaria izquierda anormal, beri beri, rabdomioma o la forma cardiaca de la enfermedad glicogénica. En los niños menores de seis meses. estos casos se confunden con la forma aguda de la fibroelastosis endocárdica por sus manifestaciones bruscas de disnea, cianosis y cardiomegalia, por lo que debe hacerse un estudio cuidadoso, investigando caracteres distintivos en cada uno de los padecimientos citados para hacer el diagnóstico correcto.

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CHANGING PATTERNS OF RESPIRATION IN NEWBORN INFANTS

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PNEUMOGRAPHIC tracings reported upon in a previous study suggested that newborn infants changed their pattern of breathing as they grew older.[1] Within a few minutes after birth and for several hours thereafter expansion of all parts of the chest and abdomen appeared to be synchronous. Eventually this pattern was replaced by one in which either the lower, anterior part of the chest wall was pulled inwards or the whole anterior chest wall was drawn downwards as well as inwards during expansion of the abdomen. It was postulated that the new patterns were the result of diaphragmatic contractions which increased in vigor and amplitude as the infant matured, thus causing the chest to be retracted during inspiration. Since the above postulate was based on pneumographic tracings which measured only the direction in which various parts of the chest and abdomen were moving, it was felt desirable to measure the force as well as determine the direction of movement of the chest and abdominal walls. The present study was consequently concerned with attempts to measure specific vectors of the chest and abdomen. In addition, clinical observations have been made on the movements of the chest and abdomen in a group of newborn and older infants to determine whether the patterns of breathing as shown by the pneumographic tracings could be differentiated simply by inspection of the infant.

METHODS

Two corrugated, hollow rubber tubes about 10 cm. in length made by Phipps and Bird and designed for pneumographic studies on small animals were used in these experiments. Prior to their use the wire springs inside the tubes were removed. The tubes were connected by a Y-tube which in turn was connected to a Marey capsule, which had a volume of about 7 to 8 cc. An ink-writing lever was used to record the movements of the rubber diaphragm of the Marey capsule. The movements of the lever were recorded on a kymograph moving at a speed of about 10 cm./min. The tubes were first placed across the front of the chest, one tube being just above the nipples and the other just below. After the chest record was made, the tubes were shifted to the abdomen and were placed transversely across it just above the umbilicus. In the latter position the tubes were touching each other. A second recording of the chest and abdomen was made in each infant immediately upon completion of the first test. The total record amounted to approximately 10 min. in each infant, about equally divided between chest and abdomen. The records were obtained with the infant resting or asleep. If the infant moved or cried, the recording was temporarily interrupted until the infant was again quiet or asleep. Most of the infants slept during the recording. During the early stages of the study the tubes were lightly but firmly held in place by straps passed around the trunk and attached to the tubes. Later a standardized procedure was adopted in which each tube was reduced to its minimum volume before being placed and then was strapped to the chest or abdomen in such a way as to increase the volume of each tube by 3 cc. This procedure made no essential difference in the results, but the data obtained under the standard conditions seemed to be more uniform. A picture of the apparatus used is shown in Fig. 1. The height of the deflections produced by the writing lever was measured to the nearest millimeter. The average height of the deflections was taken as the measure of the vector. The only change in the apparatus during the period of study was the elasticity of the rubber diaphragm.

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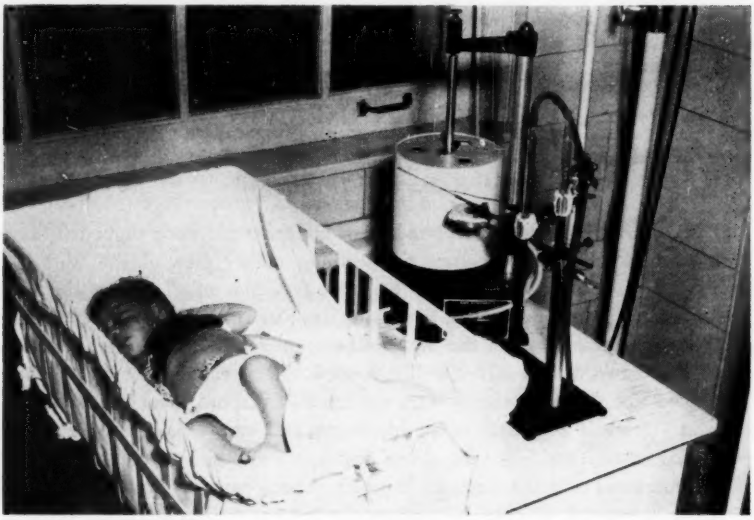

FIG. 1. Apparatus used for measuring chest and abdominal vectors.

The diaphragm was renewed every 2 or 3 wk. to preclude loss of elasticity from deterioration of the rubber.

I. Results: Measurements of Chest and Abdominal Vectors.

Forty-three tests were done on 16 normal full term infants. Eight of the infants were tested using the standardized procedure for placing the tubes on the chest and abdomen. The results of the measurements of the sample vectors of the abdomen and chest are shown graphically in charts 1 and 2, respectively. As shown in chart 1 abdominal vectors were measured on 14 infants on day of birth; 11 of these infants showed significant increases in magnitude of their abdominal vectors on subsequent tests during the first five days of life. In the remaining three infants, there was either no increase (Mo), a decrease (Ti), or an increase followed by a fall (Go). In spite of these exceptions the average height of the vectors for the group showed a 50% increment on the fifth day of life over that obtained for day of birth. In some infants the increase in abdominal vectors amounted to 100% in the first 3 or 4 days of life. The two infants who had tests done beginning on second and fourth days of life (Co and Oa) had large abdominal vectors comparable to the rest of group tested on corresponding days.

The data on chest vectors for the above group of infants are shown graphically in chart 2. It is obvious from inspection of chart 2 that there was a marked tendency for the chest vectors to fall below the zero line with increasing age. Vectors that were less than zero indicate that the segment of chest being measured was reduced in volume during inspiration. By watching the baby breathe during the test period it was easy to note when deflections of the writing lever were recording vectors less than zero. All but one of the vectors measured on day of birth were well above the zero line. Infants retested on 3, 4 and 5 days of life showed significant decreases in the size of their vectors. Several had vectors on the 4 and 5 days that had fallen well below the zero line. Tests were not continued beyond the fifth day except in one case, as babies were discharged from the hospital

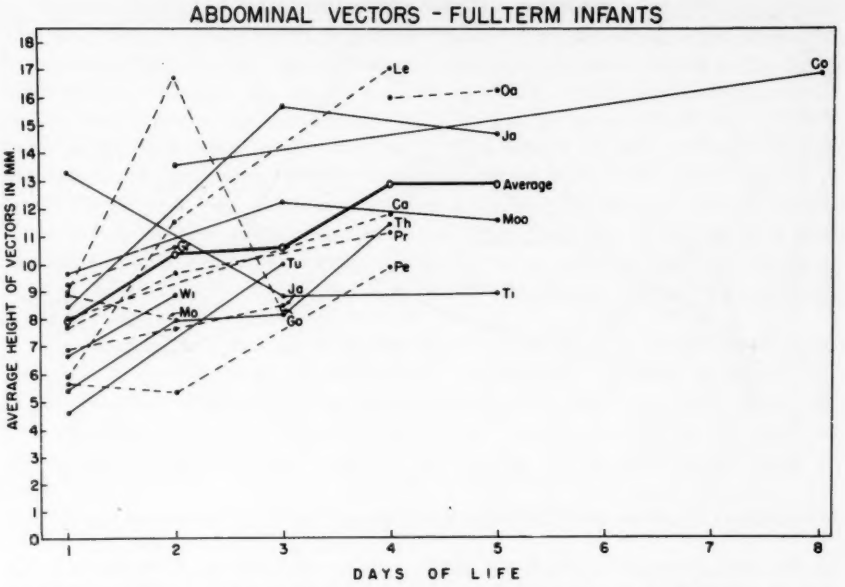

CHART 1. Solid lines and broken lines indicate, respectively, infants for whom pneumographs were and were not adapted by standardized procedure. Letters indicate names of infants.

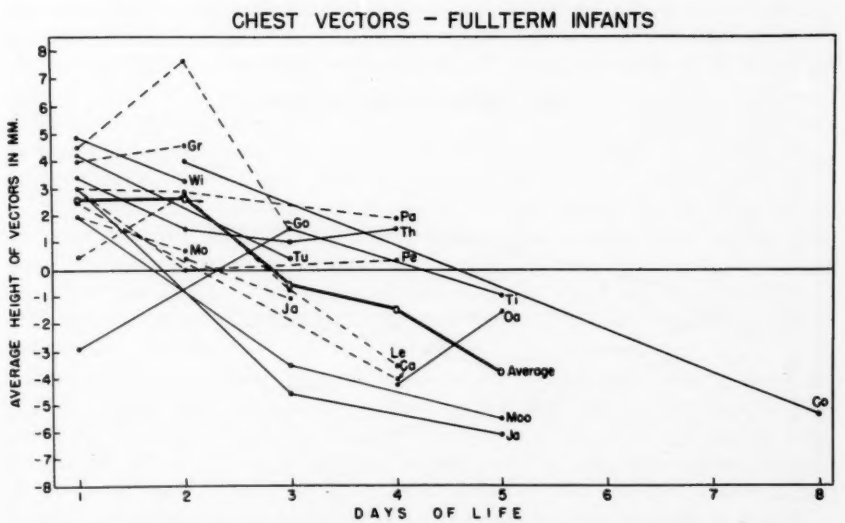

CHART 2. Solid lines and broken lines indicate, respectively, infants for whom pneumographs were and were not adapted by standardized procedure. Letters indicate names of infants and correspond to those in chart 1.

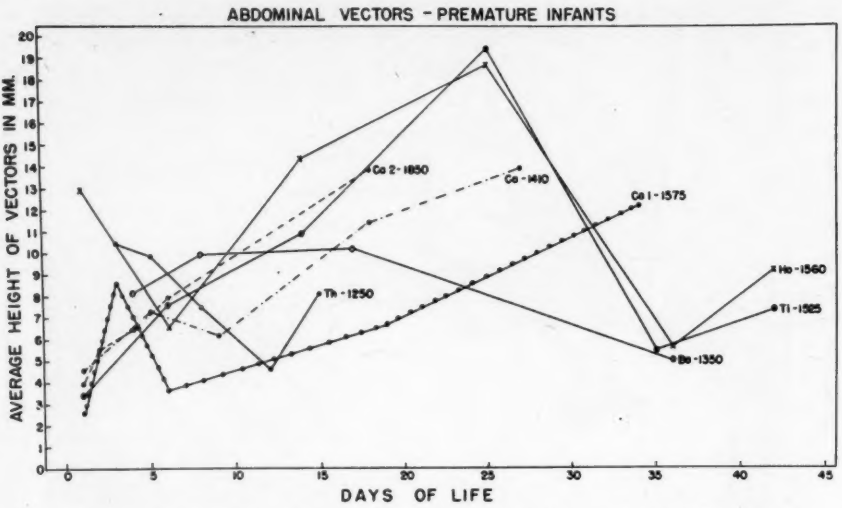

CHART 3. Birth weight is indicated to right of last test. Infants are identified by letters.

at this time. Attempts to obtain tracings in infants several weeks old were made, but considerable difficulties were encountered, as the older infants did not tolerate the apparatus and much crying ensued. In newborn infants such resistance was rarely encountered.

Thirty-three determinations were obtained on seven premature infants ranging in age from a few hours to 42 days. Data on the abdominal vectors are shown in chart 3 and those for the chest in chart 4. There was a general tendency for abdominal vectors to increase following birth, as shown in chart 3. The one infant who failed to exhibit any increase in the size of its abdominal vector, Th, had the lowest birth weight (1,250 gm.) in the

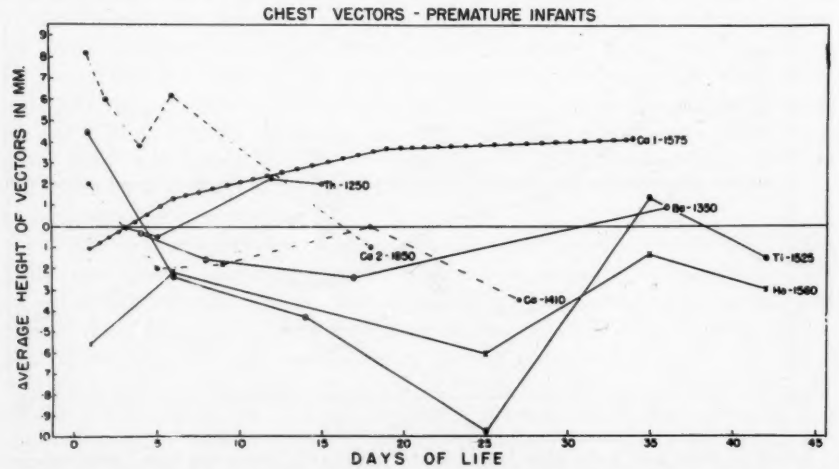

CHART 4. Birth weight is indicated to right of last test. Infants are identified by letters, which correspond to those in chart 3.

group. One other infant, Ca1 showed a slow irregular increase. It is interesting to observe that in both these infants the chest vectors increased in amplitude instead of decreasing as expected (chart 4). The size of abdominal vectors of five infants tested on the day of birth with one exception, Ho, ranged from 2.5 to 4.5 mm. as compared to a range of 4.5 to 13.3 mm. found in full term infants (chart 1). The premature infants were followed for a much longer period of time than the full term infants and some of them exhibited increases in their abdominal vectors 3 to 6 times as great as those observed on the day of birth. The increases were observed to continue up to the 34th day of life in one infant. Three infants, however, showed significant and marked decreases in amplitude of their abdominal vectors; one, after the 17th day and the other 2, after the 25th day of life. In all three of these infants the decrease in magnitude of the abdominal vector was accompanied by an opposite change in the size of the chest vectors.

It is apparent from what has been pointed out in the previous paragraph and from inspection of chart 4 that the chest vectors tend to change in a direction opposite to that of the abdominal vectors. The exceptions have already been noted. It is interesting to note that one premature infant, Ca2, had a chest vector of 8.2 mm. on the day of birth. This was almost twice the size of any chest vector found on a full term infant on the day of birth. The fact that the abdominal vector on this infant was less than 4.0 mm. on the day of birth and the chest vector was twice as large suggests that the thorax was compensating for the relatively inactive diaphragm.

II. Results: Clinical Observations.

Eighty-five healthy full term infants were observed on 213 occasions in order to observe the pattern of respiration. Almost all the infants were born spontaneously and their mothers had nitrous oxide and oxygen with or without a saddle-block. Following birth the infants cried quickly and spontaneously, were symptom-free and had no difficulties of any kind. The observations were made over a period from birth to the seventh day. Each observation consisted in counting 100 respirations and noting the incidence of the various types of respiration. It was not always possible to classify a particular respiration. Doubtful patterns were excluded. Inspection was carried out with the infant lying on his back with chest and abdomen exposed; all infants were either asleep or quiet. A group of older infants attending the well-baby clinics was likewise observed.

Respirations fell into three general patterns: (1) "synchronous," in which the anterior chest and abdominal walls appeared to expand and contract together; (2) "simple retraction," in which the lower anterior chest wall was pulled in as the upper chest and abdomen expanded; (3) "see-saw," in which all of the anterior chest wall was pulled inwards and downwards as the abdomen expanded. The three types are pictorially represented in Figs. 2, 3 and 4.

The incidence of "see-saw" pattern is shown in table 1. It increased from 2% on the day of birth to about 50% beginning on the third day and continuing so until about the third and fourth week when its incidence began to diminish markedly. The "synchronous" pattern predominated on the day of birth and the first day afterwards. All 34 infants observed on the day of birth and 44 of 45 infants seen on the day following birth exhibited "synchronous" breathing during all or part of the test period of 100 respirations. Fifty-eight infants less than 24 hours of age were observed and all breathed with "synchronous" pattern; 4 of the 58 shifted into "see-saw" pattern temporarily during test period; none showed evidence of "simple retraction." As infants became older, it was common to

see them shifting from one pattern to another while counting 100 respirations. About half of the infants over 5 days old showed this tendency during the test-period. As the incidence of "see-saw" breathing decreased in infants several weeks of age so did the tendency to shift respiratory patterns.

The variety of breathing labelled "simple retraction" in which the lower end of the sternum and the adjacent costal margins were pulled in during inspiration was not observed in any well infant less than 24 hours of age. Beginning after this time a mild form of "simple retraction" was observed; its incidence appeared to increase with age, so that by

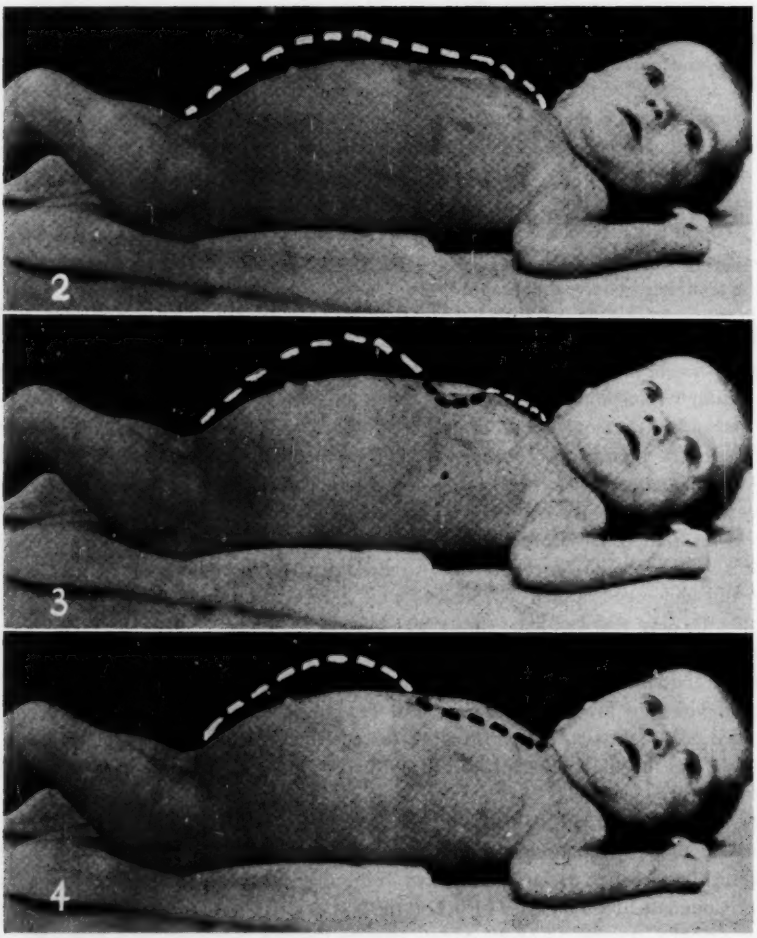

FIG. 2. "Synchronous" breathing. All anterior parts of chest and abdomen expand and contract together.

FIG. 3. "Simple retraction." Lower end of sternum and adjacent costal margins are drawn in as upper chest and abdomen expand.

FIG. 4. "See-saw" breathing. Anterior chest wall is drawn down as well as inwards as abdomen expands.

TABLE 1

INCIDENCE OF "SEE-SAW" RESPIRATIONS AND OF INFANTS SHIFTING RESPIRATORY PATTERNS ACCORDING TO AGE

Infants	Age												
	Days								Weeks				
	Birth Day	1	2	3	4	5	6	7	1–2	3–4	5–8	9–12	13–
Total	34	45	26	25	23	22	21	17	18	8	39	14	21
Per cent of total respirations that were "see-saw"	2	8	29	47	65	40	33	68	49	38	5	3	9
No. of infants shifting patterns of respirations	1	7	7	7	5	9	9	7	15	0	2	1	0

the time infants were a few weeks of age it was the predominant pattern and readily recognized. Its incidence is not shown in table 1, because there was difficulty at times in deciding whether respirations were of the "synchronous" pattern or "simple retraction."

Clinical observations were made on a small group of healthy premature infants. In general the patterns of breathing in these infants followed the same course as observed in full term infants.

DISCUSSION

There seem to be four distinct stages of respiration through which all healthy newborn infants pass. These stages can best be differentiated by the patterns of respiration that are present and to some extent by the age of the infant.

The first stage is concerned with the establishment of postnatal respirations and lasts but a few seconds or minutes after birth. This stage was not studied during the present investigation and will not be commented upon further.

The second stage begins a few minutes after birth and lasts several hours or a day or two. It is characterized in the quiet or sleeping infant by easy, smooth, synchronous expansion and contraction of all parts of the chest and abdomen. The rhythm is unusually regular as compared to the stage that follows. Even though the respiratory rate in this stage has a wide range, the rhythm remains comparatively regular at all rates. Respiration in this period has an adult quality to it except for the fact that there is little or no pause between breaths.

The third stage may be said to begin when the "see-saw" pattern or "simple retraction" make their appearance. The "see-saw" pattern may be seen occasionally during the first 24 hours of life; the authors have interpreted its presence during the first 24 hours as an indication that the third stage has begun in such infants sooner than in most. The incidence of "see-saw" breathing increases rapidly after the first 24 hours, so that by the third day it accounts for half the respirations. All infants exhibit this pattern sooner or later. It is not to be considered as an abnormal one. "Simple retraction" also makes its appearance during the third stage. In this pattern the lower end of the sternum and adjacent costal margins are drawn inwards as the upper chest and abdomen expand. In its mildest form it is difficult to differentiate from "synchronous" breathing at times. As the

infants become older, it is easier to differentiate between the two, since the retraction becomes more pronounced. By the time the age of 3 or 4 weeks has been reached it is one of the predominant patterns. The third stage is characterized not only by the appearance of these two patterns, but also by other patterns which are even more irregular and difficult to describe than the two just mentioned. It also is characterized by bizarre and irregular rhythms and considerable fluctuation in rates. The third stage appears highly unstable as compared to the second and fourth stages. There is much shifting back and forth from one pattern to another and changing in rates and rhythms. As the infant grows older, the "see-saw" pattern and the other irregular patterns and rhythms disappear.

The fourth stage is entered upon when respiratory rhythms once more become regular and the infant breaths either in "synchronous" fashion or with "simple retraction." Usually this does not occur until the infant is several weeks old.

It should be emphasized that the descriptions of stages 2 and 3 were based on a group of infants whose mothers had received relatively small amounts of analgesia and anesthesia. Consequently the babies were alert and responsive following birth. The authors have not had the opportunity to study the respiratory patterns of infants whose mothers were heavily sedated prior to delivery and hence do not know that the descriptions given apply equally to infants with initial and marked respiratory depression following birth.

Awareness of these four stages has been of help in appraising newborn infants clinically, especially in the hours immediately following birth. The appearance of any form of retraction except the "see-saw" pattern in a quiet or sleeping infant anytime during the first 24 hours of life has in the authors' limited experience presaged serious difficulties for the infant. However, the clinical experience has not been large enough to permit a final evaluation on this point. It would appear improper from the present observations to describe an infant as being well who exhibited retraction of the chest in any form, except as mentioned above, during the 24 hours following birth. This is mentioned because it is not uncommon for some infants dying with pulmonary hyaline membranes to be described as being well for the first few hours after birth and then subsequently developing retraction, cyanosis and dyspnea. Perhaps more frequent and more critical evaluations of such infants would reveal that retraction was actually present in a less pronounced form earlier than was previously appreciated.

In a previous study the authors postulated that various patterns of breathing could be accounted for by the degree of diaphragmatic tone and activity.[1] The present data on the abdominal vectors confirm the earlier contention that the vigor and amplitude of diaphragmatic contractions increase significantly during the first five days following birth. It is probably this increase in the vigor of diaphragmatic contractions which accounts for the gradual appearance of "simple retraction" after the first day or two of life. Conversely the comparatively weak diaphragmatic contractions probably explain the absence of "simple retraction" in well infants during the first 24 hours of life. However, it is not certain that all the changes can be explained by the degree of diaphragmatic activity. There are other factors which suggest the possibility that tone of the intercostal muscles may be actually lessening at the time diaphragmatic activity is increasing. In the "see-saw" pattern the whole chest appears toneless during inspiration; the anterior chest wall is drawn downwards and judging from the chest vectors the circumference of the chest is reduced during inspiration even though the diaphragmatic contractions are small at times. The rapid and frequent shifting back and forth from "see-saw" type of breathing to other patterns in which the chest plays a more positive role suggests a lack of stability in the

innervation of the muscles producing expansion of the chest. Some such lack of stability in the innervation of the intercostal muscles would help explain the fact the third stage is a temporary phase preceded and followed by stages in which the chest is obviously contributing consistently in a positive way to inspiration.

Summary

The respiratory activity of quiet and sleeping healthy infants has been studied by pneumographic tracings and by clinical observations. Four successive stages of respiration have been described through which all healthy, full term newborn infants pass.

The first stage is concerned with the establishment of postnatal respirations and lasts for a few minutes following birth.

The second stage lasts from several hours to a day or more. Respiratory activity is characterized by a wide range of rates, a regular rhythm and a single respiratory pattern, to which the term "synchronous" has been given. The term is based on the fact that all parts of the chest and abdomen expand and contract together in an easy, smooth and regular fashion. Any signs of chest retraction indicate that the infant either is not well or has passed into the third stage.

The third stage lasts several days or weeks. Infants in this stage exhibit rapidly fluctuating rates, variable rhythms and a wide variety of respiratory patterns. Two of the common patterns seen in this stage have been given the terms "simple retraction" and "see-saw." In simple retraction the lower end of the sternum and adjacent costal margins are pulled inwards as the abdomen and upper chest expand. In "see-saw" breathing the whole anterior chest wall is pulled inwards and downwards as the abdomen expands. There is much shifting back and forth from one pattern to another.

The fourth stage begins several weeks after birth and is characterized by a return to more stable rhythms and respiratory patterns. All previous bizarre patterns have disappeared, leaving "synchronous" and "simple retraction" as the only patterns of breathing.

The same four stages of respiration have been identified in a small group of surviving premature infants.

Knowledge of these stages has made it possible to give a more accurate prognosis during the first 24 hours of life on the infant's chances for survival The absence of retraction during stage 2 has been associated with an excellent prognosis for the infant. The presence of any degree of retraction in the first 24 hours of life, except as it may occur in the first few minutes after birth, has been associated with serious illnesses in the infants in the small series of cases observed to date.

Factors which might explain the presence of stages 2, 3 and 4 have been explored only partially. One of the factors involved in the change from stages 2 to 3 is the increasing vigor of diaphragmatic contractions.

Reference

1. Miller, H. C., and Behrle, F. C., Respiratory patterns in newborn infants as determined by airflow and pneumographic studies and their possible relationship to deficient vagal mechanism, Pediatrics 10:272, 1952.

Spanish Abstract

Variaciones en el Patrón Respiratorio de los Recién Nacidos

Según los autores, los recién nacidos sanos pasan por cuatro períodos definidos en su respiración. El primero corresponde al establecimiento de los movimientos respiratorios durante los primeros minutos después del nacimiento. El segundo dura de unas cuañtas horas a un día o más y en él el

ritmo respiratorio cuando el niño duerme o está tranquilo, es relativamente regular, independientemente de la frecuencia; los movimientos de las paredes torácica y abdominal son sincrónicos en todo el ciclo respiratorio y uniformes entre una respiración y otra. El tercer período ofrece un marcado contraste al anterior pues en él hay muchos ritmos, frecuencias irregulares, los movimientos del tórax y del abdomen son bruscos, se observan "respiración en serrucho" y retracciones diversas, así como variaciones acentuadas en la amplitud de los movimientos diafragmáticos; estas alteraciones en el ritmo, la frecuencia y los tipos respiratorios en el mismo niño se suceden en períodos de segundos o minutos durante un lapso que puede durar varias semanas. Al cabo de éstas se presenta el cuarto, durante el cual el ritmo respiratorio se regulariza nuevamente y los movimientos se hacen suaves, sincrónicos, aunque en ocasiones se puede observar retracción del apéndice xifoides durante la respiración.

El conocimiento del patrón característico del segundo período ayuda a la valorización clínica de las condiciones del niño; así, al observársele respirar tranquila y rítmicamente, debe esperarse que no existan anormalidades; por el contrario, la retracción del apéndice xifoides y del reborde costal, aún en grado mínimo, significa según la experiencia de los autores, la presencia de algún proceso patológico grave y alta mortalidad. Se necesitan mayores estudios para darle su significación completa a esta retracción.

La contracción vigorosa del diafragma en el tercer período es una de las diferencias con el segundo, y explica en parte la "respiración en serrucho" y la retracción ligera durante ese tercer período; la "respiración en serrucho" se ve en el 4 a 5 por ciento de recién nacidos menores de 24 horas de edad y su significado puede ser o una enfermedad potencial, o bien el paso al tercer período más rápidamente que en el resto de los niños. La retracción ligera no debe considerarse normal durante las primeras 24 horas de la vida, pues si existe demuestra alguna dificultad cardiorespiratoria; después de las 24 horas de vida, la retracción aparece gradualmente como un signo normal de la actividad diafragmática.

Los autores reconocen la necesidad de más estudios para obtener una explicación correcta de las diversas etapas respiratorias que ellos describen.

University of Kansas Medical Center

STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT

IV. Antibody Formation in the Premature Infant

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EARLY investigators have noted that the ability of infants to form antibodies improves with age. It has been a matter of speculation as to whether this improvement results from maturation of the antibody-forming system, so-called "serologic maturity," or from previous experience with antigens. This subject has been reviewed by Baumgartner.[1] Recent investigators have verified the observation that antibody formation improves with age[2,3] during infancy and placed it on a more precise quantitative basis. This was done by following the antibody response to a single injection of a potent diphtheria toxoid. The reasons for using this system have been previously discussed.[3]

In the present study, this same technic was applied to the premature infant. Because of the susceptibility of the premature infant to infection, it was felt desirable to learn something about his ability to form antibodies. In addition, the authors hoped that by studying the premature infant some information might be gained on the relative importance of maturation and previous exposure in the improvement of antibody formation that takes place with age. The approach to this second question was based on the following assumptions:

The premature infant at birth and the term infant at birth differ in maturity. However, they differ little in their previous exposure to antigen since they have both been well protected *in utero*. Any difference in antibody formation between these two groups should be due to a difference in maturity.

On the other hand, the premature infant as he approaches what should have been his normal birth date should approach the level of maturity of the term infant at birth. But by virtue of his premature birth, he will by this time have been exposed to antigens far more than the term infant. A difference in antibody formation between these two groups should be a measure of the effect of previous exposure.

METHOD

Methods of immunization and antibody-titration have been previously described.[3] Briefly, each infant was immunized with a single injection of a potent diphtheria toxoid (100 Lf on alum). Blood was withdrawn at intervals thereafter and antibody titre measured. Thirteen premature infants with birth weights varying from 1210 to 1800 gm. were immunized soon after birth. All were 12 days of age or younger except for 2 infants. Infants with circulating antitoxin by passive transfer from the mother were excluded since this may interfere with antibody production. Antibody response was compared with that of a group of term infants immunized at birth, most of whom have been previously reported upon.

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* Fellow of The National Foundation for Infantile Paralysis.

TABLE 1

PREMATURE INFANTS IMMUNIZED AT BIRTH

	Birth Weight (gm.)	Age at Immunization (days)	Antibody Titre—Months After Immunization		
			1 mo.	2 mo.	3 to 4 mo.
1.	1210	4	<.002	.04	
2.	1280	16	<.002	<.002	<.002
3.	1400	7	<.002	<.002	.04
4.	1470	5	<.002	.008	.02
5.	1480	20	.02	.1	
6.	1500	1	.1	.5	
7.	1500	12	<.002	<.002	
8.	1550	6	<.002	<.002	<.002
9.	1570	12	—	—	.1
10.	1580	5	<.002	.008	.008
11.	1630	8	<.002	<.002	.03
12.	1675	5	<.002	.01	
13.	1800	12	—	—	<.002

Cases 4 and 10 and 7 and 12 were twin births.

Another group of 7 premature infants with birth weights varying from 1240 to 1765 gm. were immunized shortly before discharge from the premature unit. At this time, they had reached a weight of 2250 to 2350 gm. and were from 1 to 2 mo. of age. This time roughly approximated what should have been their normal birth date. Antibody response of this group of infants was compared to that of term infants immunized at birth and also to term infants immunized at 1 mo. of age.

RESULTS

Results are presented in tables 1 through 4.

Statistical analysis revealed no significant difference in antibody response between premature infants and term infants immunized at birth. On the other hand, premature infants immunized about the estimated normal birth date were definitely superior in titre to term infants at birth, but were not significantly different from term infants immunized at 1 mo. of age. (For statistical analysis, see Appendix.)

TABLE 2

FULL TERM INFANTS IMMUNIZED AT BIRTH

	Age at Immunization (days)	Antibody Titre—Months After Immunization		
		1 mo.	2 mo.	3 to 4 mo.
1.	14	<.002	.006	.03
2.	7	<.002	.02	—
3.	7	<.002	.03	.05
4.	7	<.002	.004	—
5.	14	<.002	.02	.1
6.	13	.02	.1	—
7.	6	<.002	.1	—
8.	11	<.002	<.002	.1
9.	7	.006	.02	.03

TABLE 3

PREMATURE INFANTS IMMUNIZED AT ESTIMATED NORMAL BIRTH DATE

	Birth Weight (gm.)	Estimated Prematurity (days)		Age at Immunization (days)	Antibody Titre—Months After Immunization	
		From Menstrual History	From Birth* Weight		1 mo.	2 mo.
1.	1240	54	77	60	.008	.15
2.	1275	—	77	60	.02	.20
3.	1330	—	70	52	.01	.01
4.	1390	77	70	64	.04	.10
5.	1620	77	63	57	.008	.04
6.	1675	67	63	42	.02	.10
7.	1765	—	56	27	.03	—

* Calculated from curves by A. Reiche, reprinted in *Premature Infant* by Julius H. Hess and Evelyn C. Lundeen, Philadelphia, J. P. Lippincott Company, 1941, p. 21. Forty weeks was used as normal gestation period.

TABLE 4

FULL TERM INFANTS IMMUNIZED AT ONE MONTH OF AGE

	Antibody Titre—Months After Immunization		
	1 mo.	2 mo.	3 to 4 mo.
1.	$<.002$	.15	.10
2.	.004	.10	.20
3.	$<.002$	.10	.20
4.	$<.002$	.04	—
5.	$<.002$	.01	—
6.	.01	.10	.10
7.	.10	.25	—
8.	.03	.10	.75
9.	.03	.15	.05
10.	.02	.20	.15
11.	.006	.01	—

DISCUSSION

First inspection of the results would suggest that the premature infants immunized at birth responded poorly as compared to the term infants at birth. Three of the premature infants had no detectable antibodies 3 to 4 months after immunization whereas all of the newborn infants had a demonstrable titre by two months after immunization. However, statistical analysis demonstrated that this apparent difference could easily be due to chance. Figures from a similar study in the literature were examined.[4] This more than doubled the number of infants in the two groups. Once again, while the premature infants appeared to do more poorly than the term infants, the difference was too slight to be statistically valid at a 95% confidence level. And so, while it is possible that maturation during the last 2 to 3 months of gestation may improve antibody formation somewhat, the effect cannot be very great.

To evaluate the second factor, that of exposure, the group of premature infants im-

munized shortly before discharge from the premature unit (this being near their normal expected date of birth) was compared with the term infants immunized at birth. The former group gave a significantly better response than the latter. This indicates that infants exposed to extrauterine life improve more rapidly in their ability to form antibodies than infants *in utero*. This may well mean that exposure to antigens plays a significant role in the improvement.

It is admittedly difficult if not impossible to estimate what should have been the normal birth date of a premature infant with any great accuracy. Despite its faults, the birth weight is the most commonly accepted index of prematurity. As can be seen in table 3, judging from the birth weight, the infants were immunized roughly at their normal expected birth date and, in some instances, appreciably sooner. In the four intances where the mother's menstrual history appeared accurate and permitted another estimate of gestation period, the conservatism of the authors' approach was confirmed.

By immunizing premature infants shortly before discharge, another piece of useful information was gained. Clinicians have often wondered as to whether the premature infant is as well prepared to cope with the outside world by the time he is discharged from the premature unit as is the term infant at birth. It appears that in his ability to form antibodies, the premature infant may at that time be even better equipped than the term infant.

The question arises as to whether the improved function resulting from exposure is due to contact with diphtheria toxin or a closely related antigen, or whether it is a nonspecific improvement in function resulting from the general stimulation of extrauterine life. It is hardly possible that these infants all had some contact with diphtheria toxin while in the premature unit; however, the possibility of contact with similar antigens cannot be excluded. If there had been such cross-immunization, a booster type of response might have been expected. The difference between a primary and booster response is obvious in older infants. Unfortunately the authors do not have similar data in this age group.

One alternative suggested to explain the improvement in antibody formation must be considered purely speculative. It appears to be a broad physiologic principle that exercise of a function may improve that function. This has long been recognized in the hypertrophy of muscles. Barnett has investigated kidney function in premature infants of the same weight but of different ages and has found better function in the older infants. Liver function in premature infants improves rapidly after birth regardless of birth weight.[7] Improved performance with usage has been demonstrated in certain enzyme systems in the chick.[6] The improvement in specific antibody formation following immunization with the specific antigen probably falls into the same category. It does not seem too far-fetched to suggest that any antigen or group of antigens that stimulate the cells to form antibodies may improve their general level of function even when responding to other unrelated antigens. Obviously the premature infant after birth is much more exposed to many types of antigen than the normal fetus of the same gestational age who is still *in utero*.

Such improvement would be expected to be at a much lower level than that following specific immunization. If this hypothesis should prove true, the converse, that of reduced function following protection from antigenic stimulation, would naturally follow. Unfortunately the authors' data cast no light on these problems.

The theoretic implications in the care of the premature infant are interesting. At present the general approach involves shielding and substituting for any deficiencies. This is frequently essential to the survival of the infant. As our knowledge grows, it may be found preferable in certain instances to improve deficient functions by putting them to use.

Summary

The antibody response of premature infants immunized at birth with a single injection of diphtheria toxoid was compared to that of a group of term infants similarly immunized. No significant difference was demonstrated.

A group of premature infants was immunized about the time that was estimated to be their normal birth date and the antibody response compared to that of term infants at birth. The performance of the premature infants was superior to that of the term infants.

The significance of these findings is discussed.

Acknowledgment

The authors are indebted to Miss Martha Roberts, R.N., and her staff, and to Mrs. Gloria Hirsch for their assistance in obtaining the necessary specimens.

Appendix

The statistical analysis by Dr. Donald Mainland and Mrs. Lee Herrera of the Division of Medical Statistics of the Department of Preventive Medicine, New York University—Bellevue Medical Center, is as follows:

The significance level adopted throughout was the 5% level (P, the probability of chance occurrence, less than 0.05).

First the infants were classified according to presence or absence of detectable titre. At 2 mo. after immunizations, and at 3 to 4 mo., no significant differences were found. The analysis of the titres 1 mo. after immunization was as follows:

Class	Time of Immunization	Titre 1 Mo. After Immunization	
		Less Than .002	More Than .002
Prematures	Birth	9	2
Prematures	Estimated date of birth (E D B)	0	7
Term*	Birth	5	2
Term	1 mo. after birth	4	7
Term	3 mo. after birth	1	5

* Two term infants immunized at birth (case numbers 7 and 8) have been added since this analysis. Their responses parallel those already analyzed and would not affect these results.

The chi-square test for homogeneity in this gave $\chi^2 = 15.99$, which has a probability less than 0.01. Since most of the expected values in the chi-square calculation were less than 5, it was desirable to use Haldane's[8] method. This gave $\xi = 2.807$ with a probability 0.0025, very like the result of the chi-square. There is no doubt about the heterogeneity. It is therefore possible to make individual comparisons, thus:

Class	Time of Immunization	Titre 1 Mo. After Immunization	
		Less Than .002	More Than .002
Prematures	Birth	9	2
Term	Birth	5	2
	Difference not significant; P greater than 0.05		
Prematures	E D B	0	7
Term	Birth	5	2
	Difference significant at 5% level; P = 0.021		
Prematures	E D B	0	7
Term	1 mo.	4	7
	Difference not significant at 5% level		
Prematures	Birth	9	2
Prematures	E D B	0	7
	Difference significant at 1% level; P = 0.0022		

In order to make use of the actual measurements, the titres were transformed into logarithms. Those with titre below 0.002 (zero, or at least not detectable) could not be used; but the question was posed: "In those infants that show a detectable titre at the one month stage, do the five classes (or any of them) differ significantly in the titre (mean titre)?"

If such a difference could be shown, it would tend, perhaps, to confirm the contrast between the prematures immunized at the estimated date of birth and the term infants immunized at birth, demonstrated above. There was no suggestion of a significant difference, P being greater than 0.20. (In this analysis, the infant with titre 0.1 (premature infant immunized at birth) was omitted to avoid a possibly misclassified infant; but unless there were more figures than are available here, we should not feel justified in concluding that this figure was really out of line.)

It seemed possible that some of the groups might differ from others in rate at which their titre increased after it became detectable. Therefore, in those that showed a detectable titre at the first month a comparison was made with the titre in the same infants at the second month after immunization (mean increases in titre). The five classes showed no suggestion of difference in rate of increase, P being greater than 0.5.

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Spanish Abstract

Estudios Sobre la Inmunología del Recién Nacido

IV. Formación de Anticuerpos en el Prematuro

La capacidad del organismo para formar anticuerpos mejora con la edad; esta mejoría puede deberse a la maduración progresiva del sistema inmunitario, la llamada madurez serológica, o bien a la sensibilización resultante del contacto previo con los antígenos. El presente estudio se realizó para observar la capacidad del niño prematuro para formar anticuerpos, así como analizar la importancia que en él tienen, para mejorar ese sistema de defensa, tanto la maduración del sistema inmunitario como sus exposiciones a los diversos antígenos.

Este segundo problema se abordó considerando a priori que la madurez del niño prematuro y la del recién nacido, tomados al nacer, no es la misma, ya que difieren bien poco en lo que respecta a su exposición previa a antígenos, pues ambos han sido protegidos in utero. Cualquier diferencia en la formación de anticuerpos de estos dos grupos sería debido a diferencia en madurez; y al llegar a la fecha de su nacimiento normal, el niño prematuro tendría la madurez del recién nacido a término, a su nacimiento. Pero su nacimiento prematuro le ha proporcionado mayor oportunidad que al niño recién nacido, de término, de exponerse a los antígenos y, por lo tanto, la formación de anticuerpos en ambos grupos podría ser diferente; esta diferencia sería un índice del efecto que en los prematuros tuvieran las exposiciones previas.

El estudio se realizó con trece niños prematuros inmunizados con una inyección de toxoide diftérico (100 Lf en aluminio) y su respuesta se comparó a la de un grupo de niños nacidos a término e inmunizados también al nacer.

Otro grupo de siete prematuros de uno a dos meses de edad fué inmunizado en la misma forma y su respuesta se comparó a la de niños a término inmunizados al nacer y con niños a término inmunizados a la edad de un mes.

Estadísticamente no hubo diferencia significativa en la respuesta antigénica entre los prematuros y los niños a término, inmunizados al nacer. En cambio, los niños prematuros inmunizados en la fecha considerada como la correspondiente a su nacimiento normal, respondieron definitivamente en forma superior a los niños a término inmunizados al nacer, pero no respondieron en forma diferente a los niños a término inmunizados al mes de edad.

Estos datos sugieren, por una parte, que la maduración de este sistema de defensa en los últimos dos a tres meses de gestación es muy poco significativa; que los niños expuestos a la vida extra uterina mejoran rápidamente su capacidad de formación de anticuerpos, y por último, que el prematuro al salir de su unidad hospitalaria se defiende mejor del medio ambiente en donde va a vivir que el niño a término, recién nacido.

477 First Avenue

ABSORPTION OF FAT AND VITAMIN A IN PREMATURE INFANTS

III. Effect of Surface Active Agents on the Absorption of These Substances

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PREVIOUS studies[1] by some of the authors reported that particle size was an important variable in the absorption of lipids by premature infants. A comparison between an unemulsified preparation and a homogenized preparation containing particles no larger than two microns in diameter showed that the latter gave better absorption of both fat and vitamin A.

Since this work was undertaken considerable interest has developed in a group of surface-active agents, the "tweens," as adjuvants to fat absorption. These sorbitan polyoxyethylene esters have hydrophilic and hydrophobic groups and act as emulsifying agents, a property that should be conducive to improved lipid absorption. Data reported by Jones et al.[2] in adult steatorrheas indicated that a significant improvement of absorption could be obtained with "tween 80." However, Johnson and his collaborators[3] failed to find improved fat absorption in premature infants supplemented with this agent. Because of the relatively small number of infants studied by them it seemed desirable to extend these observations. It was also possible that the unpalatability of "tween 80" might have exercised an unfavorable effect or have masked a favorable one. Observations were therefore also made with a more palatable preparation, "tween G1205."† The present report deals with 32 controlled observations on premature infants and two observations on older children with steatorrhea.

EXPERIMENTAL PROCEDURES

Healthy premature infants between 4 and 38 days of age were employed. Complete fecal collections were obtained by use of metabolism frames or by means of plastic diapers. The metabolism periods consisted of 4 days each, stools being marked with carmine at the beginning and end of each period. In general the first period was a control period without tween; this was followed by a tween period and, finally, by a second control period without tween. In the first experiments no interval elapsed between periods. Subsequently a 48 hr. interval was introduced between each. The presence of this interval seemed in no way to affect the results.

The control feeding consisted of a standard milk formula prepared from dried cow's milk and cane sugar providing approximately the following percentage distribution of calories: protein 15% fat 35% and carbohydrate 50%. In some instances a special milk formula in which corn oil was

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* Deceased.

† Supplied by the Atlas Powder Company, Wilmington, Del.

TABLE 1

EFFECT OF TWEEN 80 ON FAT AND VITAMIN A ABSORPTION

Patient	Initial Weight (gm.)	Fat Absorption (%)			Vitamin A Absorption (%)		
		Pre-Control Period	Tween Period	Post-Control Period	Pre-Control Period	Tween Period	Post-Control Period
Panico	1300	74.2	82.4	81.0	63.75	84.	70.
Gilmore	1440	80.0	89.5	66.1	66.5	85.	65.
Henderson	1899	72.5	82.6	84.6	45.	85.	72.
Jones	1970	49.0	57.9	51.9	50.	50.	49.
Gibson	1490	77.7	83.5	81.5	60.75	62.	49.
Caramata	1200	82.3	93.4	84.1	76.5	84.	69.
Santos	879	71.6	87.2	79.6	57.5	77.	70.
Jones	1580	70.1	75.6	84.0	58.	66.	70.
Brewster	1450	68.6	77.4	88.4	65.	72.	57.
	Average	71.8	81.1	77.9	60.3	73.0	63.4

TABLE 2

EFFECT OF TWEEN G1205 ON FAT AND VITAMIN A ABSORPTION

Patient	Initial Weight (gm.)	Fat Absorption (%)			Vitamin A Absorption (%)		
		Pre-Control Period	Tween Period	Post-Control Period	Pre-Control Period	Tween Period	Post-Control Period
Jones	1580	71.5	92.6	79.4	57.5	76.0	65.0
Santos	879	70.0	77.3	84.0	58.1	73.1	70.0
Brewster	1450	68.4	85.0	88.4	65.0	58.2	57.1
Wong	1550	54.5	53.9	41.8	42.0	78.0	56.0
Scalfoni	1580	74.0	87.5	68.0	69.0	86.0	66.0
Bartelio I	1080	77.6	80.0	—*			
Brodus I	920	37.7	57.8	43.9			
Strict	1920	57.5	75.0	69.2			
Bartelio II	1420	38.4	66.5	62.5			
Brodus II	1200	45.3	67.6	60.5			
Ortega	1650	74.5	81.7	77.1			
	Average	60.9	74.9	67.5	58.5	74.0	63.0

* Specimen partially lost.

substituted for butter fat was used. This was fed at levels providing approximately 130 cal./kg. Feedings in the tween periods were identical with those on control periods except for addition of tween. Quantity of tween given was proportional to fat intake. Preliminary observations had shown that a dose of tween 40 mg./gm. fat was well tolerated; this dose was therefore adhered to. In the early experiments tween was given by medicine dropper between feedings; in later experiments it was homogenized in feedings.*

* Experimental food in which corn oil was used was prepared for the authors at the laboratories of Mead Johnson & Company through the courtesy of Dr. Warren M. Cox, Jr.

TABLE 3

EFFECT OF TWEEN G1205 ON FAT ABSORPTION

Patient	Initial Weight (gm.)	Control I (%)	With Tween (%)	Control II (%)
Romero	1690	40.8	56.4	
		40.6	64.5	
Rosado I	1985	55.0	53.0	
		61.5	74.5	
Rosado II	1515	45.8	76.0	
		86.0	92.2	
Dugan	1590	83.3	87.2	91.0
Isalde	1510	61.0	73.0	72.2
Average		59.2	72.1	

TABLE 4

EFFECT OF TWEEN G1205 ON FAT ABSORPTION IN PREMATURE INFANTS RECEIVING CORN OIL

Patient	Initial Weight (gm.)	Fat Absorption (%)		
		Corn Oil Control	Corn Oil+Tween	Butter Fat
Romero	1690	65.9	72.3	40.6
Rosado I	1985	62.8	68.8	61.5
Rosado II	1515	88.2	85.5	86.0
Dugan	1590	95.5	96.2	83.3
	Average	78.1	80.7	67.9

TABLE 5

EFFECT OF TWEEN G-1205 ON FAT ABSORPTION IN PATIENTS WITH CYSTIC FIBROSIS OF PANCREAS AND CONGENITAL BILIARY ATRESIA

Patient	Period I—(Control)			Period II—Tween Added		
	Fat Intake (gm.)	Fat Absorbed		Fat Intake (gm.)	Fat Absorbed	
		Gm.	%		Gm.	%
Gross* 8 yr. old Congenital biliary atresia	168.8	78.8	(46.6%)	168.8	91.7	(54.3%)
Pavloni* 11 yr. old Cystic fibrosis of pancreas	226.1	131.6	(58.1%)	226.1	133.0	(58.7%)

* Milk feedings with supplement of melted butter were employed in these 2 studies.

Aliquots of stool from each experimental period were assayed for vitamin A by a modification of the Carr-Price procedure.[4] The remainder of stool was dried and assayed for fat by the procedure of Tidwell and Holt.[5] Fat and vitamin A intake were similarly assayed. Vitamin A intake was derived in part from milk and in part from a supplement of oleum percomorphum given once daily. Intake varied slightly depending on size of feeding, range being between 20,000 and 22,000 units/day.

Results

These are given in tables 1 to 5. In table 1 are shown observations on nine infants who received a supplement of tween 80. It is apparent that there is approximately a 10% improvement in fat absorption and a slightly greater increase in vitamin A absorption. The values decrease after the discontinuance of the tween but do not return to the precontrol level, as might be expected in view of the slightly more mature state of the infant. Averaging the pre- and the post-control periods indicates a fat absorption of 74.9% in the controls and 81.1% for the tween periods. The vitamin A absorption in the pre- and post-control periods when averaged is 61.0% as compared to 73.0% for the tween 80 periods.

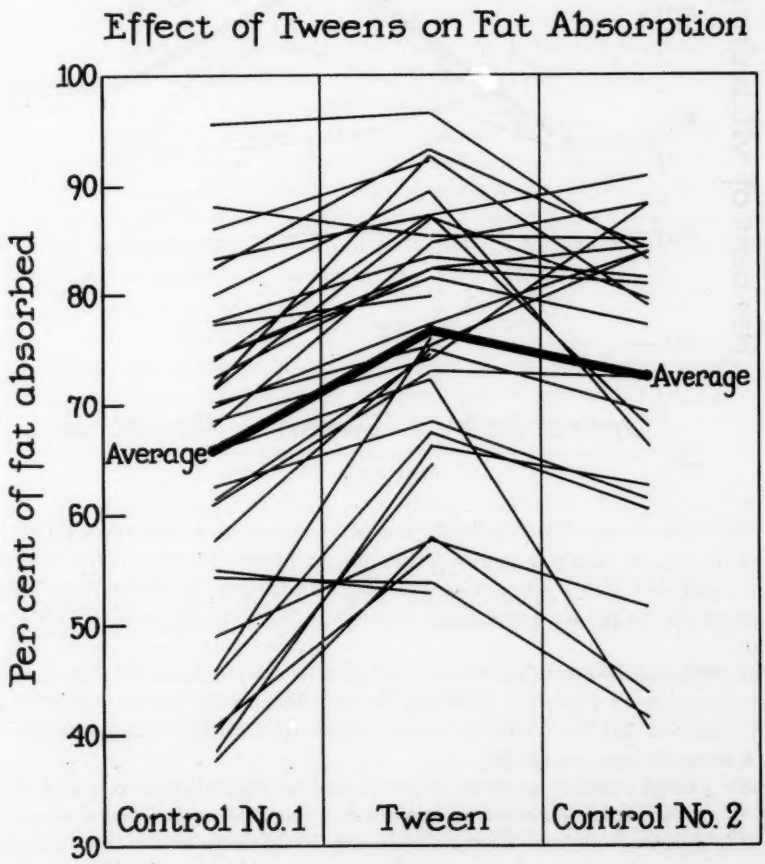

Chart 1

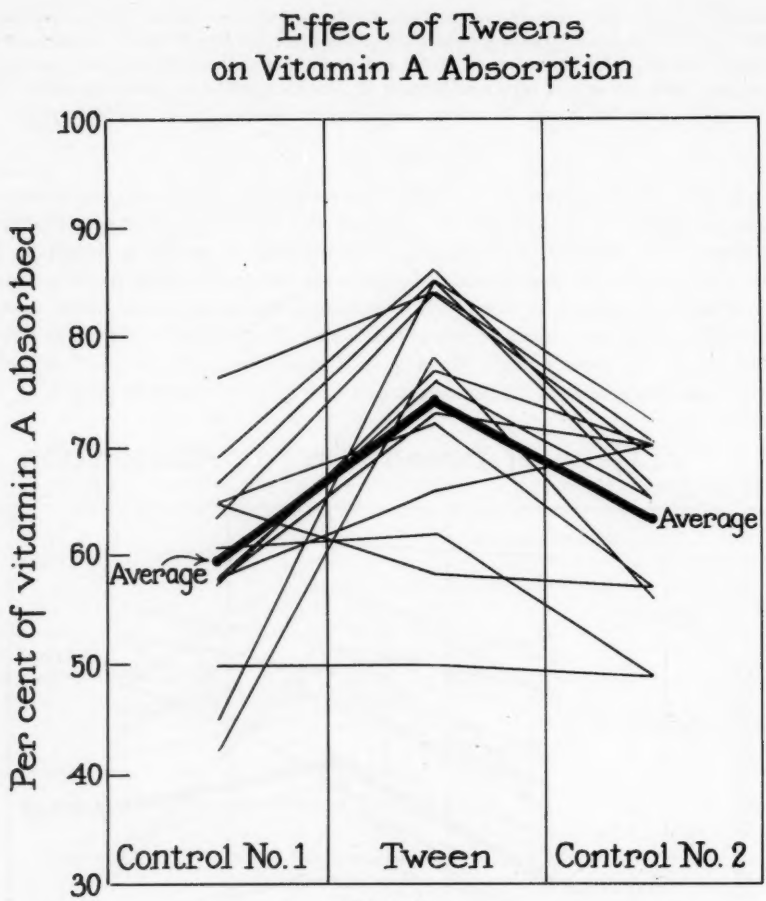

CHART 2

Table 2 shows similar findings in the case of 11 infants studied on tween G1205. An average of the pre- and post-control periods gives a figure of 64.2% for fat absorption as compared with 74.9% when tween was added. In the case of vitamin A the average absorption for the pre-and post-control periods was 60.8% as compared to 74.0% with tween.

The improved absorption on tween is not seen in every instance. In some cases the infant showed better absorption in the post-control period than in the tween period. It may also be observed that the correlation between improved fat absorption and improved vitamin A absorption is not a close one.

Table 3 shows a smaller group of infants studied subsequently who received a supplement of tween G1205. With one exception only a single pre-control period was carried out. It is apparent, however, that the findings are closely comparable to those of table 2.

It was of interest to ascertain to what extent tween would be of value in improving fat

assimilation when a more readily assimilable fat than butter fat was employed. A few observations were therefore made with corn oil, with and without tween. These are shown in table 4. Here it may be seen that with the higher percentage absorptions found with corn oil relatively less benefit results from the addition of tween.

A summary of all the data on premature infants receiving either tween 80 or tween G1205 indicates that fat absorption was increased from an average control value of 69.1% to 76.6% (chart 1) and that vitamin A absorption was increased from an average control figure of 61.4% to 74% (chart 2).

Two observations were made on older children suffering from marked steatorrhea, one, a case of congenital biliary atresia and the other, a case of cystic fibrosis of the pancreas. Both patients were on high fat diets and were gaining weight. Some measure of improvement was noted in the case of biliary atresia whose percentage absorption of fat rose from 46.6% to 54.3%. Improvement was not observed in the patient with cystic fibrosis of the pancreas.

Discussion

The results reported confirm the findings of Jones and Culver[2] in adults in regard to the improvement of fat absorption brought about by tweens in states of steatorrhea. Contrary to the observations of Johnson et al.,[3] they indicate that premature infants are no exception to the rule.

The improvement in absorption though significant is not a striking one and one may well question whether as a practical measure such a procedure is worth while in view of the fact that increased fat absorption of considerably greater degree can be brought about by other means. It can be brought about by the substitution of more readily assimilable fats for butter fat,[6] among which corn oil may now be included. It may also be effected by increasing the fat intake as the authors have shown elsewhere.[7]

Summary

Observations on premature infants have shown that fat assimilation and vitamin A assimilation can be increased by the use of either tween 80 or tween G1205. The increase is a relatively small one and of questionable practical importance.

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SPANISH ABSTRACT

Absorción de las Grasas y Vitamina A en Niños Prematuros

III. Efecto de Agentes Detergentes Sobre la Absorción de Estas Substancias

En un estudio previo, los autores observaron que el tamaño de las partículas de los lípidos es un factor importante para su absorción en los niños prematuros; las grasas y la vitamina A de una mezcla homogeneizada, con partículas no mayores de 2 micrones de diámetro, fueron absorbidas más fácilmente que las de otra mezcla sin emulsionar. De este trabajo nació el interés de ver el efecto en la absorción de las grasas, de substancias detergentes, las llamadas "Tweens," ésteres con grupos hidrófilos e hidrófobos que actúan como agentes emulsionantes, propiedad que facilitaría la absorción lipoídica. En efecto, esto se ha observado en adultos con esteatorrea, usando el "Tween 80"; pero no así en prematuros con este mismo agente (Johnson y colaboradores) por lo que los autores del presente artículo trataron de ampliar el número de casos estudiados. El "Tween 80" es de sabor muy desagradable que pudo haber ejercido efectos desfavorables, o bien ocultado mejores respuestas; por lo tanto, en esta experiencia se empleó además, una preparación de mejor sabor, el "Tween G 1205."

Las observaciones en este grupo de prematuros mostraron que realmente hay mejor absorción de grasas y de vitamina A con el uso del "Tween 80" o del "Tween G 1205," pero en forma tan discreta que su importancia práctica es dudosa si se consideran los mejores resultados de otros medios, por ejemplo, el uso de grasas de por sí más fácilmente absorbibles, como el aceite de maíz, o aumentando la ingestión de grasas.

477 First Avenue

STUDIES IN DISORDERS OF MUSCLE

IX. Glycogen Storage Disease Primarily Affecting Skeletal Muscle and Clinically Resembling Amyotonia Congenita

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MASON and Andersen[1] in 1941 reported a careful clinical, pathologic and metabolic study of two patients with glycogen storage disease of the liver and reviewed the literature. They concluded that there is a defect in glycogenolysis and in glycogen synthesis from glucose in this disorder, although it appeared that there is normal glycogenesis from galactose and fructose. On the basis of their own biochemical studies and those of others they postulated that an enzymatic defect is responsible for the accumulation of excess glycogen.

They pointed out also that it is possible to distinguish from this type of glycogen storage disease a form which primarily affects the heart and is characterized by cardiomegaly and congestive cardiac failure. Subsequently di Sant'Agnese, Andersen and Mason[2] in a study of two such cases of cardiac glycogen storage disease emphasized the lack of hypoglycemia and ketosis, as well as the finding of normal glucose tolerance curves and normal hyperglycemic response to epinephrine. This is in contrast to the findings in the hepatomegalic form of the disease.

In reviewing the reported cases of glycogen storage disease, Mason and Andersen also separated certain cases because of atypical features which made them seem different from the hepatomegalic or cardiomegalic types. Gunther[3] had described a patient in whom a clinical diagnosis of amyotonia congenita had been made but at autopsy vacuolar destruction of skeletal muscle by glycogen deposition was observed. Subsequently, Clement and Godman[4] described a child with cardiomegaly and marked hypotonia of skeletal muscles in whom the signs of congestive failure were not striking. They implied that the glycogen storage disease of heart and skeletal muscle are part of the same syndrome. A few additional reports of possibly related cases have appeared.[5-7]

The present investigators are reporting clinical and pathologic observations on two siblings with severe muscular weakness associated with destruction of skeletal muscle by glycogen infiltration but with only moderate cardiomegaly and no cardiac symptoms.

Clinical reports of patients with glycogen storage disorders have been abundant, but only a few biochemical studies have been made. Although it is repeatedly stated that the glycogen is normal in glycogen storage disease, critical evaluation shows that the conclusion is based on inadequate evidence. No definitive examination of the physico-chemical constitution of normal and abnormal human glycogen has been accomplished, as far as is known, heretofore. The authors have determined the specific rotation, molecular weight

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and degree of branching structure in glycogen obtained from biopsy and autopsy specimens from one of these patients as well as from normal individuals and patients with certain other disorders. The chain length of the liver glycogen from the patient with muscular glycogen storage disease was definitely shorter than that of the glycogens examined from other patients and normal humans.

Case Reports

Case 1, W.D. (white male 19 mo. of age). Persistent and progressive muscular weakness of extremities had been present since the age of 3 mo. He was described as "lying in bed quite limp and inactive." Retarded motor development became obvious when, at 6 mo. of age, he could not hold his head upright for more than a few seconds. He was able to sit momentarily at 9 mo. and at 14 mo. could stand only with support. Crawling was attempted in an ineffectual manner. He was never able to walk. Parents pictured movements of extremities at time of admission as "markedly inaccurate and flopping."

Past History: Pregnancy, labor and neonatal period had been normal. Birth weight was 3.2 kg. Bronchopneumonia at 6 mo. of age was treated with antibiotics. Subsequently he had increasing difficulty in swallowing solid foods and some regression of motor ability. A month before admission he had had uncomplicated rubeola.

Developmental: Despite motor impairment, he easily adapted upon stimulation. He followed objects with eyes at 6 mo. of age and could pile blocks one on another at 10 mo. Language ability was commensurate with lack of stimulus in home environment. He was able to say "baby" words at 15 mo.

Systemic Review: Gastrointestinal: Formula was changed numerous times in 1st 3 mo. because of frequent regurgitation. Evaporated milk and water seemed to satisfy best. Thereafter, intermittent emesis occurred. History of bulky, frothy or foul smelling stools was not elicited. "Enlarged thymus" was irradiated at 4 mo. of age to "decrease the obstruction" without benefit.

Central Nervous System: Episodes of convulsions, coma or cyanosis had not occurred.

Physical Examination: Temperature 37.0°C., PR 90/min., respiration 20/min. Blood pressure 90/65 mm.Hg. Occipito-frontal circumference 45.7 cm. Weight 10.6 kg. Height 86.4 cm. Chest 43.2 cm. Abdomen 38.1 cm. Grid A3-23 first premature auxodrome. Infant appeared extremely apathetic and lay prostrate on his back, only occasionally moving extremities. Protests against examination were described as "feebly brushing at examiner's hands." Brachycephalic skull had moderate frontal bossing. Face was suggestive of mongolism because of epicanthic folds and flattening of bridge of nose. Extraocular movements normal. Tongue was normal in size. Fundoscopic examination was normal. Lungs revealed a few rhonchi. Heart was normal. Liver and spleen were not palpable. Umbilical hernia was not present. Genitalia normal. Skeletal system was normal. Marked hypotonia of musculature of extremities was evident. Complete flaccidity of entire musculature was demonstrated by the ease of flexing head on body to 90° and legs on trunk to 110°. Muscle mass was diminished in volume and felt soft. Sensory system was intact.

Hospital Course: Great difficulty was experienced in preventing regurgitation and pooling of food and secretions in posterior pharynx. Constant nursing supervision, antibiotics and frequent suctioning of pharynx were used to forestall infection. An episode of oral moniliasis complicated the feeding problem. For a few days, marked foul-smelling diarrhea necessitated discontinuing oral feeding and use of intravenous fluids. After 2 mo. in hospital he succumbed to pneumonia following a severe upper respiratory infection.

Developmental studies were done during one of the more asymptomatic periods. These revealed that motor abilities were at the level of 11 mo. but that adaptive, language and personal-social achievements were markedly advanced as compared to former. Development quotient was 75, and would have been almost normal except for motor retardation. He was not mentally retarded but had gross motor maldevelopment.

Laboratory Data: Blood, urine, spinal fluid findings normal. Fasting blood glucose was 70 mg./100 cc. Serum chloride were 103 mEq./l., cholesterol 225 mg./100 cc. and phosphate 4.5 mg./100 cc. (as phosphorus). Examination for stool tryptic activity by method of Shwachman et al.[8] was normal. Urinary phenylpyruvic acid was not present. Normal eosinophil response to epinephrine.

A therapeutic trial of neostigmine (1.125 mg.) given subcutaneously elicited no changes in facies, vigor or tone of musculature.

Skull, chest, wrist, lumbar and sacral spine RGs all within normal limits. Normal EEG.

Pathologic Summary: Body was poorly nourished, length 87.5 cm. and weight about 8.2 kg. Head appeared disproportionately large because of small slender trunk and extremities. Skin and mucous membranes pale, lips dry and fissured. Subcutaneous fat measured up to 0.3 cm. in thickness. Skeletal muscles were thin and pale. Diaphragm on right was displaced upward to level of 3rd rib. Liver extended 1.5 cm. below costal edge in R midclavicular line.

Apex of heart was displaced laterally and upward so that its long axis lay horizontally.

Heart weighed 66 gm. (average normal, 56 gm.). Average thickness of R ventricle was about 1.0 mm; left 4.0 to 6.0 mm. All valves were apparently normal.

Lungs contained small masses of airless, dark red parenchyma which were interpreted as foci of atelectasis. Liver weighed 580 gm. (av. normal, 370 gm.). Parenchyma was pale but otherwise not remarkable. Gallbladder contained about 25 cc. of yellow-green bile and appeared normal. Weight of thymus was 4.0 gm. (av. normal 26 gm.). Other organs and central nervous system were normal.

Microscopic Findings: Tissue was fixed in neutral formalin, formol-Zenker's fluid and absolute alcohol. Hematoxylin and eosin and a modified Masson's trichrome stain were used on Zenker-fixed tissue and Best's carmine stain and periodic acid—Schiff (P.A.S.) technic after alcohol and Zenker fixation.

Heart: In some areas many of the myocardial fibers exhibited oval or fusiform clear spaces which usually surrounded nuclei and which, in some instances, appeared to contain fine granules. In other places these spaces appeared to be entirely empty. In some of the swollen segments the fibrillae retained their transverse striae and appeared to be compressed against the sarcolemma. When cut transversely, similar fibers appeared as thin ring-like structures surrounding central vacuoles. With the exception of slight pyknosis, nuclei appeared to be fairly well preserved. There was no evidence of necrosis, resorption of muscle fibers or of fibrosis. Degree of vacuolation was slightly greater on endocardial side than in outer portion of ventricular walls. Alcohol-fixed sections stained by Best's carmine method exhibited coarse red granules within the vacuoles and finer granules distributed along the better preserved portions of myocardial fibers.

Lungs: Samples from both lungs contained foci of purulent bronchiolitis, bronchopneumonia and partial atelectasis.

Kidneys: In sections stained with H. & E. and by trichrome method the most conspicuous alteration was swelling and vacuolated appearance of epithelium of collecting tubules. Similiar but slighter changes were observed in the thick segments of Henle's loops and in a few of the convoluted tubules. Sections stained for glycogen showed greatest quantities of positively staining granules to be present in the epithelium of collecting tubules. Small quantities were found in various portions of cortical tubules, including neck of glomeruli, and in glomerular epithelium and capillary endothelium.

Liver: Lobular structure was well preserved and there was no excess of fibrous tissue. The principal feature was pallor and foamy appearance of parenchymal cells. Distribution of glycogen was fairly uniform but slightly greater in central and mid-zones.

Skeletal Muscle: Samples were taken from diaphragm, pectoralis major, rectus abdominis and muscles of back, thigh and calf. Of all samples examined, those selected from the pectoralis major and from thigh muscles showed least severe involvement but all samples including diaphragm showed advanced degenerative changes which were characterized by extreme pallor, irregular swelling and vacuolation, associated with excessive accumulation of glycogen within the fibers. Nuclei were pyknotic within those fibers which showed the more extreme vacuolar changes. There was no evidence of necrosis or disintegration of fibers. Sarcolemma apparently persisted intact throughout. However, in a very large proportion of the fibers, sarcoplasm was represented by small clumps of strongly acidophilic substance which enveloped one or more pyknotic nuclei, remainder of the space being partly occupied by scanty fibrillar substance and scattered granules. In sections stained for glycogen many of these clear spaces were found to contain coarse and fine granules and amorphous solid masses staining strongly with Best's carmine and P.A.S. In the better preserved fibers fibrillae and transverse striae were distinct.

Smooth Muscle: Minor changes suggesting excessive storage of glycogen were observed in muscular tissue of intestinal tract and in wall of urinary bladder. Most striking vacuolation was found in small areas within urinary bladder at ureteral orifice.

FIG. 1. Case 2, N. D. Note flaccid position from which patient was unable to move without aid.

Central Nervous System: Samples of alcohol-fixed tissue from the cerebral cortex, basal ganglia, mesencephalon, pons, medulla and cervical spinal cord showed no significant pathologic alteration of parenchyma except slight perivascular and perineuronal edema. Carminé-positive granules were not found in the neurons. A few of the larger arterioles exhibited prominent accumulations of glycogen in the media (Fig. 6).

Other tissues containing an excess of glycogen as demonstrated by Best's carmine or P.A.S. were spleen, lymph nodes, intestinal mucosa and smooth muscle of small blood vesels. Histiocytes of the centers of splenic corpuscles, of cortical follicles of lymph nodes and of lymphoid nodules of intestinal mucosa contained coarse and fine granules in variable but generally small quantities.

Thymus showed reduced numbers and density of cortical lymphocytes.

Vertebral and sternal bone marrow was moderately hyperplastic with relatively increased numbers of neutrophilic myelocytes.

Case 2, N.D. (white female, 12 mo. of age). Parallel pattern of progressive muscular weakness in this patient and her sibling (Case 1) excited authors' interest. Until 2 mo. of age, regurgitation and pooling of secretions in pharynx were the only symptoms. Thereafter, pronounced motor retardation began. Although she had been able to hold head upright in prone position, to rotate body and to move extremities in newborn fashion, on admission she was not able to sit even with support, and head remained in a flexed position on chest (Fig. 1). Ineffectual attempts to grasp and to move extremities only accentuated the neonatal posture.

Past History: Gestation, delivery and neonatal period had been normal. Birth weight: 2.8 kg. Review of systems and developmental history showed no additional positive findings.

Physical Examination: Temperature 37.3°C., PR 96/min., respirations 30/min. Blood pressure 90/70 mm.Hg. Height 76.2 cm. Weight 8.6 kg. Grid A8-45-67% auxodrome. Skeletal system normal. Infant was apathetic during examination and remained quite motionless. Marked hypotonia of musculature was most prominent. Complete flaccidity of muscles of arms, legs and spine gave the impression of picking up a rag doll. Muscles felt soft and decreased in mass. Hyporeflexia symmetric. Sensation normal. Marked flattening of occiput with a prominent forehead was observed. Fundoscopic examination normal. Tongue not enlarged. Heart and lungs normal. Liver was palpated at R costal margin. Spleen and kidneys not felt.

Hospital Course: Because of liability to regurgitate secretions and food, constant vigil to prevent pneumonia was maintained. She was given penicillin prophylactically. Pharnyx was aspirated frequently. Despite this, however, she became progressively weaker and died from aspiration pneumonia at 15 mo. of age.

During these 3 mo. she smiled and laughed when fed. She was able to follow objects with eyes. Grasp was good in intention and direction but weak in strength.

Laboratory Data: Blood and urine findings were normal. Blood urea nitrogen 12 mg./100 cc., serum chloride 107 mEq./l., serum Ca 11.4 mg./100 cc., serum phosphate 5.3 mg./100 cc. (as phosphorus) and serum cholesterol 200 mg./100 cc. Serum alkaline phosphatase was 9 and 6 Bodansky units on 2 occasions. Kahn and Mantoux tests negative. A 24 hr. urine collection revealed a preformed creatinine of 145 mg. and creatine of 45 mg. (as creatinine).

ECG showed T-waves to be inverted in V_1 to V_4 and Q-T interval at upper limits of normal, suggesting myocardial damage.

Heart, lung, long bones, wrist and skull RG revealed no pathologic findings.

A therapeutic trial of neostigmine 0.5 mg., given subcutaneously, did not improve muscular tone or strength. Adenosinetriphosphate (2 mg.) given intramuscularly demonstrated no change in muscular tone. Electric stimulation of muscles revealed a normal response. Response of glucose and galactose tolerance tests as well as blood glucose and lactic acid response to epinephrine are shown in chart 1. Lack of sustained hyperglycemia in glucose tolerance tests indicated effective glycogenesis. Normal response of blood glucose to epinephrine demonstrated glycogenolysis. Ability to metabolize galactose appeared to be normal since tolerance test was normal and no reducing substances appeared

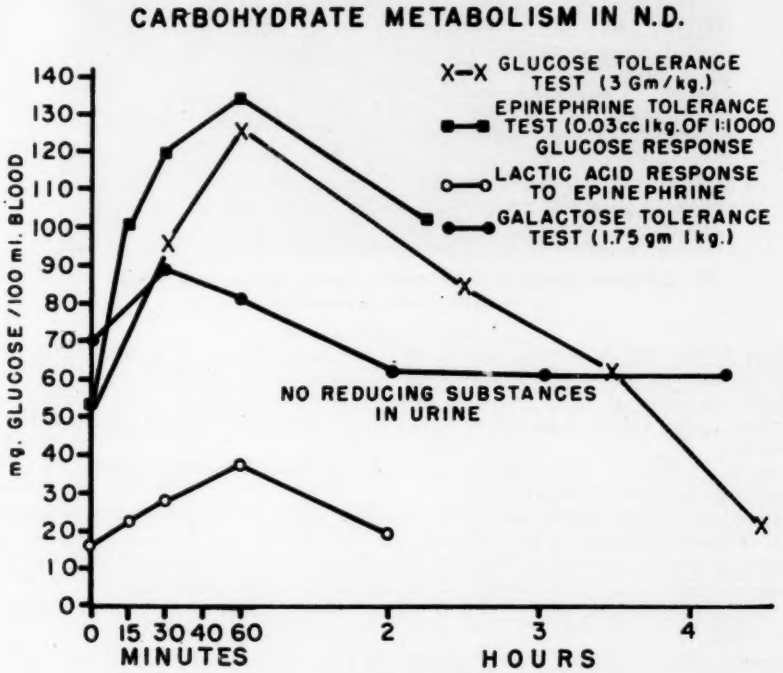

CHART 1

in urine. Normal lactic acid response to epinephrine suggested normal anaerobic metabolism of muscle glucosephosphate.

Pathologic Summary: Body well formed but slightly emaciated, length 55 cm. and weight estimated at about 9 kg. Skin and mucous membranes pale. Extremities unusually slender and skeletal muscles, particularly those of buttocks and extremities, pale and thin. Subcutaneous fat of abdominal wall measured up to 0.7 cm. in thickness. With the exception of fibrous adhesions between margin of liver and omentum (site of surgical biopsy) serous cavities appeared normal. Arch of diaphragm on each side reached level of 4th intercostal space anteriorly.

Heart weighed 66.5 gm. (average normal: 23 gm.), position and contours normal. Myocardium, endocardium and valves normal on gross examination.

Lungs presented evidence of lobular exudative pneumonia and partial atelectasis in dependent portions of both lower lobes and in apex of R upper lobe. Bronchi and bronchioles contained a small quantity of blood-tinged mucus.

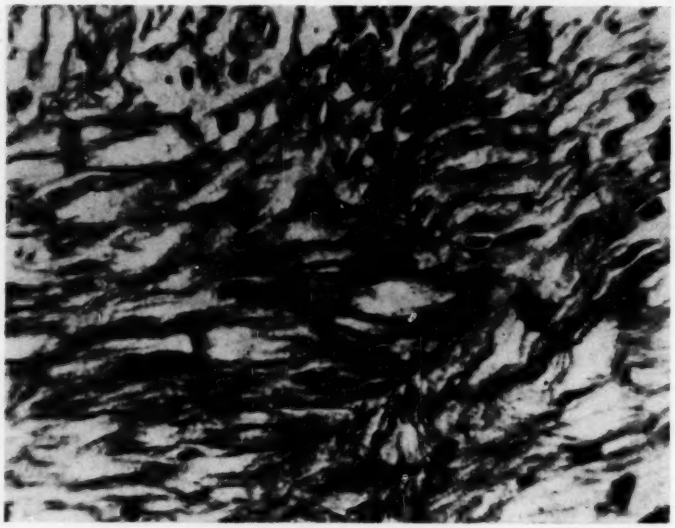

FIG. 2. Photomicrograph of cardiac muscle (Case 2) showing vacuolization, loss of striation and pyknotic nuclei.

Liver weighed 440 gm. (average normal: about 300 gm.). Capsular and sectional surfaces were pale but otherwise normal. Significant pathologic alteration was not recognized in any of the other thoracic and abdominal viscera except the relatively small size of thymus which weighed 6 gm. Adrenals together weighed 4 gm. and the thyroid 1.5 gm. Examination of central nervous system not permitted.

Microscopic Findings: Heart: Sections from both ventricles and interventricular septum showed same findings as in Case 1. (See Fig. 2.)

Lungs: Sections representing some of the more solid lesions were largely occupied by coalescent areas of bronchopneumonia. In one focus there was evidence of an older inflammatory process, characterized by presence of epithelioid histiocytes, lymphocytes, fibrous thickening of alveolar walls and masses of coarsely vacuolated macrophages within alveolar spaces (lipid pneumonia).

Liver, kidney, lymphoid tissues and bone marrow showed changes similar to those observed in Case 1 (Fig. 3).

Skeletal Muscles: Samples from diaphragm, iliopsoas, quadriceps femoris, gluteus maximus, pectoralis major and rectus abdominis muscles examined in routine and glycogen-stained sections showed advanced degenerative changes associated with excessive accumulation of glycogen similar to description of appearance of skeletal muscle above. (See Figs. 4 and 5.) More extreme degrees of degeneration were found in quadriceps femoris and least in diaphragm.

Family History and Genetics: An additional fact was revealed by family history. First infant of this marriage mirrored these cases. Family physician had noted marked muscular hypotonia in this infant. "He had never been able to hold his head up. Muscles were flabby; repeated episodes of regurgitation were the cause for frequent hospitalization, and death was due to pneumonia. Hemogram, urinalysis, chest and skull RG were all normal."

Mother had been married previously and has a normal 6 yr. old daughter by that marriage. Two siblings of mother died at 5 days of age from unknown causes. Three children described above were only progeny of father. His family history is not remarkable.

Nature of hereditary mechanism is not apparent. A neonatal metabolic disorder such as was observed in the authors' subjects, appearing repeatedly from one mating, seems most probably to have a hereditary mechanism. It is begging coincidence to suggest that a simple Mendelian recessive would appear in the only 3 offspring of heterozygous parents. Without further data it seems fruitless to speculate about the more complex genetic mechanism which might lead to these findings.

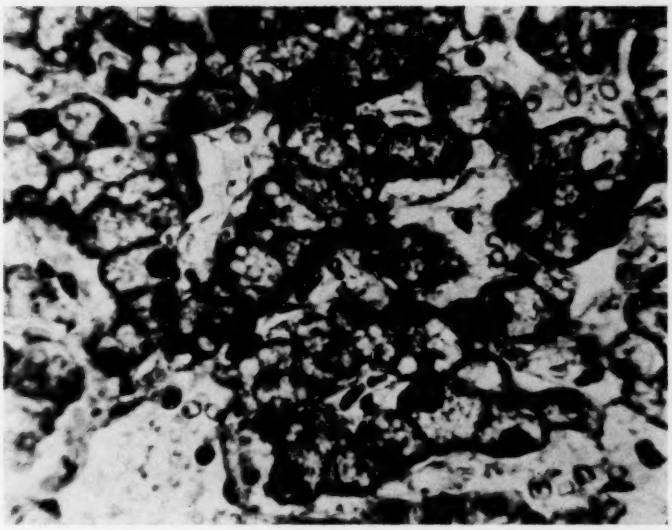

FIG. 3. Photomicrograph of liver (Case 2) showing foamy cytoplasm.

PHYSICO-CHEMICAL STUDIES

Stability of Glycogen: Biopsies of liver and muscles were taken and in order to minimize autolytic effects on tissue glycogen and enzymes, were immediately preserved at a temperature of —30°C. Sections of liver and muscles were taken as soon as possible (2 hr.) after death and were cared for similarly. Glycogen content was determined by method of Good, Kramer and Somogyi.[9] Autoglycogenolysis was allowed to occur at room temperature (23°C). Results are shown in table 1. It is apparent that some autoglycogenolysis occurred in biopsy specimens of both liver and muscle but that a plateau at 4 or 5% of wet weight was being approached, instead of complete hydrolysis as should occur in normal tissue, particularly liver. In the autopsy material a pathologic level persisted and no further glycogenolysis occurred at room temperature for 11 hr.

Physico-chemical Analysis: Muscle and liver glycogens were purified and analyzed for their specific rotation, sedimentation in ultracentrifuge and degree of branching. Details of methodology and results of the study of these glycogens as well as other human glycogens are being published separately.[10, 11]

Biopsy postmortem and specimens from patients without specific carbohydrate disorders were obtained in a similar manner. Diagnoses at time of death or operation in patients from whom control glycogens were obtained were as follows: (a) auricular paroxysmal tachycardia; (b) bulbar poliomyelitis; (c) peptic ulcer; (d) peroneal muscular atrophy.

TABLE 1

STABILITY OF LIVER AND MUSCLE GLYCOGEN IN GLYCOGEN STORAGE DISEASE OF MUSCLE (CASE 2)

Biopsy	Control	4 Hours	7 Hours	11 Hours
Liver	9.5	7.3	6.2	
Muscle	10.1	3.4	5.1	
Autopsy				
Liver	4.1			4.6
Muscle	3.4			5.4

All values expressed as grams glycogen (as glucose)/100 gm. wet weight of tissue.

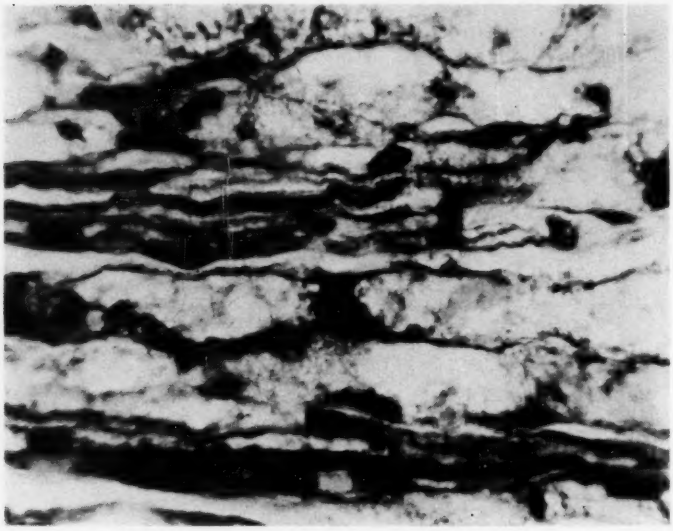

FIG. 4. Photomicrograph of skeletal muscle (Case 2) showing extreme vacuolar destruction within sarcolemmal sheath.

FIG. 5. Photomicrograph of skeletal muscle (Case 2) stained with Best's carmine showing masses of glycogen in vacuoles of muscle fibers.

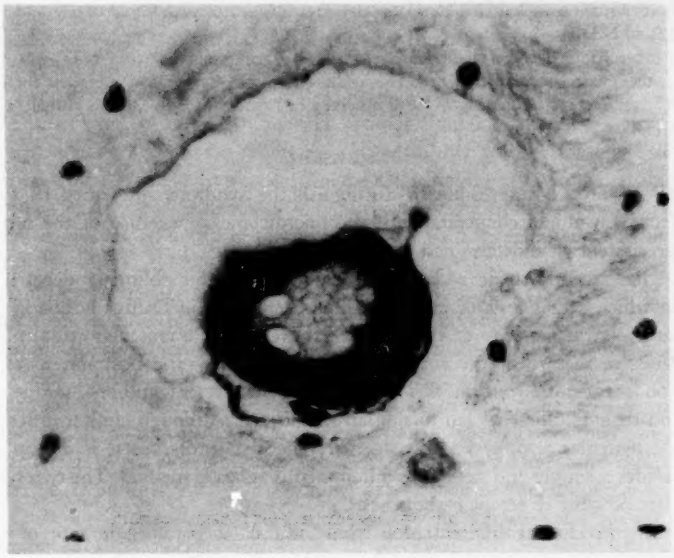

FIG. 6. Photomicrograph of arteriole in brain stained with periodic acid-Shiff technic to show glycogen deposition in smooth muscle.

Chemical purification of glycogen from N.D. showed no evidence that it was abnormal except for great increase in the amount present. Direct analysis of biopsy material showed between 10 and 11% of wet weight in muscle and slightly less in liver. Somewhat smaller recoveries reported in table 2 reflect the fact that these were prepared to obtain maximum chemical purity rather than maximum recovery. Optical rotation before and after hydrolysis were similar to other values for glycogen and glucose reported in the literature.

Ultracentrifuge and chain length data are summarized in table 2. Two very broad peaks of ultracentrifuge sedimentation were found in all samples of human liver glycogen but there was little difference between control and glycogen storage disease values. Muscle glycogen also showed 2 broad peaks, second being of smaller molecular weight and present in only quite small absolute amounts in

TABLE 2

PHYSICO-CHEMICAL PROPERTIES OF GLYCOGEN

Source of Glycogen	Glycogen Recovered /100 gm. Wet Weight	Ultracentrifuge				Chain Length by Periodate Oxidation	Per Cent Hydrolysis by β-Amylase
		Component 1		Component 2			
		S20W	Per Cent	S20W	Per Cent		
Normal Human Liver	1.6	78	64	250	36	14.0	39
	(0.1 to 2.6)	(63 to 97)	(45 to 80)	(150 to 300)	(20 to 55)	(13.5 to 15.0)	(35 to 42)
Case 2 Liver	7.7	74	65	200	35	9.5	25
	(6.3 to 13.8)	(72 to 75)	(63 to 39)		(34 to 37)		
Normal Human Voluntary Muscle	0.4	56	92	14	8	14.5	39
	(0.06 to 0.7)	(47 to 69)	(85 to 99)	(12 to 15)	(0 to 15)	(14.5 to 14.5)	(37 to 40)
Case 2 Voluntary Muscle	7.3	62	68	29	32	13.0	32
	(7.1 to 8.9)	(59 to 67)	(61 to 76)	(22 to 36)	(24 to 39)		(32 to 31)
Case 2 Cardiac Muscle	2.5	75	68	38	32		25

Values reported are summation of series of studies. Average values are given with range in parentheses. Details of individual runs may be found in separate publications.[10,11]

glycogen from normal muscle. This component was greatly increased both relatively and absolutely in material from N.D.

On the other hand, average chain length of all glycogens obtained from N.D. was shorter as judged by either periodate oxidation or beta-amylase hydrolysis than that of glycogen obtained from normals. Shortest average chain lengths were observed in hepatic glycogen of this patient with glycogen storage disease of muscle.

Discussion

Clinically, it proved impossible to distinguish the syndrome presented by these two patients from amyotonia congenita until the microscopic appearance of the muscle and its glycogen content were determined.

Brandt[12] has recently made a careful follow-up of all the siblings and patients from families in which a diagnosis of amyotonia had been made in Danish hospitals. He concluded that the great majority of these patients have infantile muscular atrophy resulting from progressive disease of the anterior horn cells. Biopsy and postmortem pathologic investigation seemed to confirm this impression. The present authors' studies of such patients and their families has led to similar conclusions. Although clinical differentiation of infantile muscular atrophy and glycogen storage disease of muscle is difficult, muscle biopsy provides a simple and definitive differential diagnostic method. The two syndromes obviously are of quite different pathogenesis.

In contrast, the clinical differentiation from the usual hepatomegalic type of glycogen storage disease is simple, but the proof of pathogenetic differences between the types of glycogen storage disease is more difficult. The authors have presented some studies on glycogen from a patient with hepatic glycogen storage disease,[10, 11] which show it to be more like normal glycogen than that obtained from the patient with glycogen storage disease of muscle. In addition, the lack of hypoglycemia, ketosis and impaired glucose

TABLE 3
Types of Glycogen Storage Disease

	Hepatomegalic	Muscle Cases	Cardiomegalic
Clinical Manifestations			
Hepatic enlargement	++	±	±
Hypoglycemia	+	−	−
Ketosis	+	−	−
Cardiac enlargement	−	+	++
Cardiac failure	−	−	+
Muscular weakness	±	++	+
Age of onset	2 mo. to 10 yr.	1st mo.	1st mo.
Usual age at death	variable-frequently adolescence	before 2 yr.	2 to 3 yr.
Glycogen content of liver (Normal 1 to 4%)	15 to 16%	9%	5 to 10%
Glycogen content of muscle (Normal <1%)	usually less than 1%	10 to 11%	10 to 11%
Alterations of physical character of glycogen	? change in proportion of molecule species	short chain length	?
Glucose tolerance test	prolonged	normal	normal
Galactose tolerance test	normal	normal	normal
Epinephrine tolerance test (lactic acid and glucose response)	flat	normal	normal
Postmortem autoglycogenolysis	none	partial	? complete

tolerance in the present syndrome emphasize the probable differences in mechanism. The cardiomegalic type of glycogen storage disease, on the other hand, has many similarities to the disorder presented in this report. Table 3 is derived from the authors' clinical experience and the reports of glycogen storage disease in the literature and will serve to emphasize these similarities and differences. Studies similar to these in a case of cardiomegalic glycogen storage disease might help to settle this point. At present the bulk of the evidence would seem to justify the clinical classification of glycogen storage disease into two main varieties, a hepatomegalic type characterized by hypoglycemia and ketosis and a primary muscle type which may be associated with cardiac symptoms or muscular weakness.

Several lines of evidence have led previous authors[1] to postulate that deficiencies of the enzymes concerned in the intermediary metabolism of carbohydrate may be responsible for the abnormal accumulation of glycogen in glycogen storage disease. Inconclusive evidence has been presented that phosphorylase may be deficient in the hepatomegalic form of glycogen storage disease.[13] The present studies of the glycogen from a patient with the muscle type of glycogen storage disease shows that it has an abnormal physical structure characterized by an excess of branched linkages in the glycogen and shorter average chain length than normal glycogen. A simple explanation of this finding would be that the "de-branching" enzyme system described by Cori and Larner[14] was present in insufficient amounts to allow normal degradation of glycogen. The resulting accumulation of glycogen might produce mechanical injury to the cell. Such a thesis is consistent with the fact that a review of the literature shows that nearly every value which appears to be technically accurate shows approximately 16% glycogen in the liver in the hepatomegalic cases and approximately 10% in the muscle in cardiomegalic cases. As has already been emphasized, the present case is similar to the latter group.

On the other hand, the clinical observation of markedly impaired function of skeletal muscle but normal hepatic function is in contrast to the lesser degree of abnormality in muscle glycogen than in liver glycogen. This apparent paradox may be related to the lower level of phosphorylase activity found in muscle as compared to liver, thus allowing the chain on the abnormally abundant branches to retain a more nearly normal length. Thus, the total mass of glycogen is increased more rapidly in muscle. In addition, the muscle would appear to be unable to tolerate a higher concentration of glycogen. These two factors could result in the initial damage in the muscle rather than liver in the muscle type of glycogen storage disease. Only carefully controlled studies of the enzymatic content of liver and muscle from normal human subjects and from patients with glycogen storage disease will serve to settle this problem. These studies, however, offer a working hypothesis which can be evaluated by methods which are available.

Conclusions

Three infants (siblings) with flaccid weakness of skeletal muscle are described with postmortem findings in two. Clinically, the disease simulated amyotonia congenita (Oppenheim's disease), but the anatomic disorder in these infants consisted of excess glycogen storage producing its main effect in striated muscle.

Muscle biopsy is essential in the differential diagnosis of the muscular atrophies of infancy.

This disorder has many similarities to the cardiomegalic type of glycogen storage disease and may be contrasted with the more common hepatomegalic (von Gierke's) type.

Glycogen isolated from the tissues of one of these patients showed excess branching and decreased average chain length. There was an excess of a low molecular weight component in the skeletal muscle.

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SPANISH ABSTRACT

Estudios en Trastornos Musculares

IX. Enfermedad Glicogénica que Afecta Fundamentalmente los Músculos Esqueléticos

Como hasta la fecha se han realizado pocos estudios bioquímicos en los pacientes con enfermedad glicogénica, no se tiene una valoración crítica concluyente todavía sobre la normalidad del glicógeno. Los autores de este artículo hicieron observaciones clínicas y patológicas en tres niños con debilidad muscular glicogénica y discreta cardiomegalia sin manifestaciones cardiacas; aprovecharon los casos para realizar algunos estudios sobre la rotación específica, el peso molecular y la estructura del glicógeno obtenido de muestras de biopsias y la autopsia de dos de estos pacientes, comparándolos con individuos normales y enfermos de otros trastornos.

Desde el punto de vista clínico fue imposible diferenciar el síndrome de estos casos de la amiotonia congénita, lo que se logró por biopsia determinando el aspecto microscópico de los músculos y su contenido de glicógeno; ya Brandt había dicho que los casos de amiotonía congénita tenían atrofia muscular por lesión de las astas anteriores. La biopsia muscular es, pues, un método diagnóstico diferencial definitivo ya que los dos síndromes presentan una patogenia diferente.

En contraste, la diferenciación clínica con la forma común hepatomegálica de la enfermedad glicogénica es muy sencilla, pero la demostración de la diferente patogenia entre ambos tipos sumamente difícil; en cambio el tipo cardiomegálico tiene muchas similitudes con el tipo muscular. Esto sugiere la posibilidad de dividir clínicamente la enfermedad glicogénica en dos grandes variedades: el tipo hepatomegálico caracterizado por hipoglicemia y quetosis, y el tipo muscular, comprendiendo tanto los casos de manifestaciones cardiacas como los de trastornos de debilidad muscular.

Los estudios del glicógeno en los casos de estos autores muestran una estructura física anormal, consistente en un exceso de uniones dentro de la molécula y una cadena más corta que la del glicógeno normal, hallazgos explicables por la teoría de Cori y Lorne de una deficiente actividad enzimática de degradación; la acumulación de glicógeno lesionaría la célula. Por otra parte, la disfunción muscular opuesta a una función hepática normal—en estos casos—contrasta con el mayor grado de anormalidad del glicógeno hepático, paradoja explicable por la fosforilación inferior observada en el músculo que en el hígado, que permite mayor acúmulo de glicógeno en la masa muscular y menor tolerancia al mismo, de lo que resultaría más lesionada la célula muscular que la hepática en la variedad muscular de la enfermedad glicogénica. Es necesario que se realicen más estudios sobre la actividad enzimática del hígado y los músculos, tanto en sujetos normales como con este padecimiento.

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BRONCHIAL OBSTRUCTION WITH LOBAR ATELECTASIS AND EMPHYSEMA IN CYSTIC FIBROSIS OF THE PANCREAS

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AS THE name cystic fibrosis of the pancreas implies, emphasis was initially placed on the pancreatic rather than the respiratory lesions. Steatorrhea and malnutrition were the clinical features that first attracted attention and the pathologic findings in the pancreas were distinctive and quite consistent. Consequently the anatomic changes in the pancreas are well recognized and the altered physiologic mechanisms due to the absence of pancreatic enzymes relatively well understood.[1-5]

However, a variable degree of bronchial and pulmonary involvement is a virtually constant feature of the disease, usually dominates the clinical picture and determines the fate of the patient.[6] The morphologic changes in the respiratory system at necropsy have been well described by a number of authors.[1, 5, 7, 8] It should be remembered, however, that these represent the terminal results of severe chronic bronchial and pulmonary infection and not necessarily or to the same degree the changes present in living patients. Postmortem findings, furthermore, give only slight insight into the mechanisms responsible for the respiratory involvement.

It is the purpose of this paper to discuss clinical material bearing on some aspects of the respiratory component of fibrocystic disease of the pancreas.

I. DESCRIPTION OF CASES

In the 12 years from 1939 through 1951, 211 patients with cystic fibrosis of the pancreas have been seen at Babies Hospital. Diagnosis was established in all cases by duodenal drainage or postmortem examination or both. Twenty-two (10.4%) of the 211 cases presented on roentgen examination of chest atelectasis involving one or more pulmonary lobes during the course of first episode of pulmonary involvement.

In two additional patients, lobar atelectasis accompanied a sudden worsening of a long-standing respiratory infection and represented a terminal complication. The two latter cases will not be included in the analysis which follows.

Important clinical, laboratory and postmortem findings of the 22 patients under consideration have been summarized in table 1A (15 fatal cases) and table 1B (7 cases still active). For the sake of clarity, both groups will be discussed together and case numbers from 1 to 22 have been assigned to the patients.

1. Age and Mode of Onset.—All patients were white; 14 were male and 8 female. In 18 cases, lobar collapse was present on admission; in 4 it developed during hospitaliza-

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tion. In 15 of the 22 cases, symptoms of respiratory involvement appeared before the age of 3 months and in 21 before 6 months of age. One patient (Case 7) was free of respiratory symptoms until 5½ years of age. Lobar atelectasis was recognized roentgenographically in 11 patients before the age of 3 months and in 18 before 6 months of age. The time interval between onset of coughing and recognition of lobar collapse on roentgen examination of the chest was less than 1 month in 15 and less than 3 months in 18 of the 22 cases. On the supposition that atelectasis had been present for some time before chest RGs were taken, an even shorter time than indicated by the figures may well have elapsed between onset of respiratory symptoms and development of lobar collapse.

In 13 cases the chief complaint on admission related only or primarily to the respiratory symptoms; in 5 of these, respiratory distress and cyanotic spells had been noted. In only 4 instances, abnormal stools were the chief presenting complaint. Three patients had been operated on shortly after birth for meconium ileus.

2. Laboratory Findings.—Duodenal contents were assayed for pancreatic trypsin in 15 cases. Tryptic activity was virtually absent or markedly reduced in all instances (normal values with this viscosimetric method >100 u./cc.).*

Serum carotene levels were determined on first admission in eight cases and in all were below the normal lower limit (40γ/100 cc.).* A low carotene is an expected finding in cystic fibrosis of the pancreas, as intestinal absorption of carotene is poor in the presence of steatorrhea.

Serum vitamin A levels were found to be within normal limits in 7 of the 10 cases in which they were determined during first admission (normal levels $>$ 30 I.U./100 cc.).* Such levels are frequently normal despite impaired intestinal fat absorption because they reflect the administration of substantial amounts of preformed vitamin A. This explanation of normal serum vitamin A levels is further borne out by the observation that the two patients who had abnormally low levels were seen at a time when vitamin supplements were not given routinely as in recent years.

3. Nature and Distribution of Pulmonary Lesions.—The consistency of the distribution of the atelectasis on chest RGs was striking (tables 1A and 1B). In no case was the left lung affected, in 17 only one lobe of the right lung and in 5, more than one lobe. The right upper lobe was the most frequently involved, the right middle lobe next, and the right lower lobe was never involved alone.

Atelectasis persisted unchanged throughout the severe phase of the illness until death or improvement in 14 cases; in 2 it shifted from one lobe to another, and in 6 it cleared only to reappear in the lobe previously affected. This was explained by the finding at post mortem that in only 2 of 11 patients examined was the atelectasis organized. In both of these children, lobar collapse in RGs had been present without change for more than 1 year. This lack of anatomic organization in most cases also explains the lack of correlation between clinical and anatomic findings of atelectasis in some instances.

In 15 cases, bronchopneumonic changes were seen on RGs on admission and were roughly proportional to the duration of the pulmonary disease as evaluated from the clinical history. Seven patients who gave a history of coughing, and who had lobar atelectasis on RGs, failed to exhibit the usual clinical and laboratory signs of infection. In these children a normal total white count and differential, a normal sedimentation rate and lack of fever bore out the absence of extensive inflammatory changes in the lungs

* Methods used and normal values have been previously described.[9]

at this time. Even in them, clinical and laboratory signs of severe bronchial and pulmonary infection eventually developed and at autopsy suppurative bronchitis and lobular pneumonia were constant findings. In 5 cases, multiple lung abscesses were present as well.

TABLE 1A

CLINICAL, LABORATORY AND POSTMORTEM DATA ON 15 PATIENTS WHO DIED

Clinical Data								
Case No.	Sex	Year of Birth	Chief Complaint on Admission	Age: Onset of Respiratory Disease	Age: Atelectasis First Seen on X-Ray	Age: Death	Total Duration of Illness	Antibiotic Agents Administered†
1. (S.2)*	F	1938	Coughing	4 wk.	12 wk.	16 wk.	12 wk.	0
2. (S.3)	F	1939	Resp. distress	7 wk.	8 wk.	10 wk.	4 wk.	0
3. (S.7)	M	1939	Coughing	22 wk.	25 wk.	34 wk.	12 wk.	Sulfathiazole
4. (S.8)	M	1939	Poor wt. gain	10 mo.	14 mo.	15 mo.	21 wk.	Sulfathiazole
5. (S.15)	M	1942	Coughing	6 wk.	10 wk.	16 wk.	10 wk.	0
6. (S.24)	M	1942	Cough, poor wt. gain	8 wk.	17 wk.	26 mo.	24 mo.	Sulfadiazine; penicillin
7. (S.31)	M	1938	Foul stools	5 6/12 yr.	5 10/12 yr.	5 11/12 yr.	5 mo.	Penicillin
8. (S.88)	M	1947	Resp. distress	3 wk.	6 wk.	14 wk.	11 wk.	Sulfadiazine; penicillin Streptomycin
9. (S.89)	F	1943	Cough, foul stools	13 wk.	3 6/12 yr.	3 9/12 yr.	3 6/12 yr.	Sulfadiazine; penicillin Bacitracin
10. (S.90)	M	1947	Meconium ileus	4 wk.	8 wk.	12 wk.	8 wk.	Penicillin
11. (S.105)	M	1948	Coughing	6 wk.	8 wk.	23 wk.	17 wk.	Sulfadiazine; penicillin
12. (S.107)	F	1947	Meconium ileus	14 wk.	Infancy	2 4/12 yr.	25 mo.	Sulfadiazine; penicillin Streptomycin Aureomycin
13. (S.109)	M	1948	Resp. distress	16 wk.	17 wk.	19 wk.	3 wk.	Sulfadiazine; penicillin
14. (S.127)	M	1948	Coughing	25 wk.	26 wk.	15 mo.	9 mo.	Sulfadiazine; penicillin Aureomycin
15. (S.154)	M	1949	Cyanotic spells	2 wk.	22 wk.	52 wk.	50 wk.	Sulfadiazine; penicillin Streptomycin Aureomycin Polymyxin B

* Numbers in parentheses refer to series numbers assigned to patients with cystic fibrosis of pancreas in chronologic order of their admission to Babies Hospital.

† Penicillin and streptomycin administered by IM injection and inhalation; bacitracin and polymyxin B only by inhalation.

Squamous metaplasia of bronchial epithelium was present in only 2 of 11 cases examined at postmortem.

In all patients but one (Case 22), emphysema was either present on admission or developed during the course of the disease. With the exception of one case (Case 17), the emphysema affected all portions of the lungs not collapsed. In 4 cases it was determined by fluoroscopy to be obstructvie and not compensatory in nature. In the other 16, respiratory distress, cyanosis, and often shift of the mediastinum in the direction opposite to that of the atelectatic lobe suggested the presence of a ball-valve type of bronchial obstruction.

4. Course of the Illness.—The following case reports demonstrate some of the clinical features of three patients with lobar atelectasis accompanying cystic fibrosis of the pancreas.

CASE REPORTS

S.D. (Case 19), a white female infant, was admitted at the age of 9 days with the chief complaint of vomiting, which was never satisfactorily explained. The subsequent course of the patient's illness on the wards of Babies Hospital is summarized in Fig. 1. In a routine chest RG on admis-

sion, the findings were normal (Fig. 2A). On the 7th day after admission, coughing began unaccompanied by other evidences of infection. The temperature, total and differential white count as well as the sedimentation rate, were normal. After 3 days of coughing, severe cyanosis and respiratory distress set in

TABLE 1A

(Continued)

Clinical Data—*Continued*									Pertinent Autopsy Findings					
Lobar Atelectasis on Chest RGs						Pancreatic Trypsin (viscosimetric units/cc.)	Serum Levels		A.	B. Lungs§				
Lung Involved		Lobe Involved			Character of Atelectasis		Carotene γ/100 cc.	Vit. A I.U./100 cc.	Pancreas	Lobar Atelectasis				Squamous Metaplasia of Bronchial Epithel.
Right	Left	RUL	RML	RLL						Organized	RUL	RML	RLL	
+	0	+	0	+	Persistent	—	—	—	C.F.P.‡	0	+	0	+	+
+	0	+	0	0	Clearing partly	—	0	0	C.F.P.	0	+	0	+	0
+	0	+	0	0	Persistent	1.7	1	0	—	—	—	—	—	—
+	0	0	+	0	Persistent	0.0	4	1	C.F.P.	0	0	0	0	0
+	0	+	0	0	Persistent	—	—	—	C.F.P.	0	0	0	0	0
+	0	0	+	0	Persistent	0.8	0	30	C.F.P.	+	0	+	0	0
+	0	+	+	+	Persistent	7.7	2	90	—	—	—	—	—	—
+	0	+	+	0	Persistent	—	—	—	C.F.P.	0	+	+	0	0
+	0	0	+	0	Persistent	—	—	—	C.F.P.	0	+	+	0	0
+	0	+	+	+	Clearing	3.3	—	—	C.F.P.	0	0	0	0	0
+	0	0	+	0	Persistent	1.4	0	56	C.F.P.	0	0	+	0	0
+	0	+	0	0	Altern. clearing	4.4	0	48	C.F.P.	+	0	+	0	0
+	0	+	+	+	Persistent	—	—	—	C.F.P.	0	+	+	+	+
+	0	+	0	0	Altern. clearing	13.0	32	111	C.F.P.	0	0	0	0	0
+	0	+	0	0	Clearing	1.6	0	42	—	—	—	—	—	—

‡ Changes typical of cystic fibrosis of pancreas.
§ All patients at autopsy presented diffuse lobular pneumonia and emphysema.

and the patient was placed in an oxygen tent where she remained for over 3 wk. A film of the chest at this time showed atelectasis of the RUL and no evidence of inflammatory changes in the remainder of the lungs (Fig. 2B). The atelectasis, a few days later, was found to have shifted to the RML (Fig. 2C). Obstructive emphysema was suspected because of the patient's respiratory difficulty. It was only 1½ wk. after onset of cyanosis and respiratory distress that the temperature and total white count rose to significant levels and the patient exhibited the other laboratory signs of an acute infection (Fig. 1). The obstructive emphysema and the bronchopneumonic changes were evident in a film of the chest at this time (Sept. 19). About 4 wk. after the onset of respiratory symptoms, the temperature and white count gradually returned to normal, the respiratory difficulty slowly disappeared. Penicillin, aureomycin and streptomycin aerosol were given throughout. Nose and throat cultures on 3 occasions yielded Staph. aureus hemolyticus, mannitol and coagulase positive. One year later, a chest film was normal. Two weeks after admission, at the age of 3½ wk., pancreatic trypsin was found to be less than 1.4 u./cc. Duodenal assay 2 yr. and 3 mo. later showed exactly the same level of this enzyme.

G.V. (Case 13), a 5 mo. old white male, had been without any complaints until 2 wk. before admission to Babies Hospital in 1948; in particular, his state of nutrition was good. At that time he had developed a mild cough without other signs of infection and was thought to have a mild upper respiratory infection. Six days before admission, he had suddenly developed signs of consolidation in

TABLE 1B

Clinical and Laboratory Data on 7 Patients Who Are Living

Case No.	Sex	Year of Birth	Chief Complaint on Admission	Age		Lobar Atelectasis on Chest RGs						Pancreatic Trypsin (viscosimetric units/cc.)	Serum Levels		Antibiotics Administered†	Present Condition‡
				Onset of Respiratory Symptoms	Atelectasis First Seen on X-ray	Lung Involved		Lobe Involved			Behavior of Atelectasis		Carotene (γ/100 cc.)	Vit. A (I.U./100 cc.)		
						Right	Left	RUL	RML	RLL						
16. (S.52)*	M	1945	Diarrhea since birth	11 wk.	11 wk.	+	0	0	+	0	Persistent	3.6	0	96	Penicillin Streptomycin Chloromycetin Aureomycin Terramycin	Chronic bronchopneumonia
17. (S.55)	F	1945	Foul stools	8 wk.	14 wk.	+	0	+	0	0	Cleared at 5 mo.	1.0	—	—	Penicillin	Doing well
18. (S.133)	F	1948	Resp. difficulty	8 wk.	8 wk.	+	0	+	0	0	Altern. clearing	<1.4	—	—	Penicillin Aureomycin	Chronic bronchopneumonia
19. (S.146)	F	1949	Vomiting	2 wk.	3 wk.	+	0	+	+	0	Clearing at 5 mo.	<1.4	—	—	Penicillin Streptomycin Aureomycin	Doing well
20. (S.183)	M	1950	Meconium ileus	3 wk.	3 wk.	+	0	+	0	0	Clearing at 8 mo.	1.8	—	—	Penicillin Streptomycin Aureomycin Terramycin Chloromycetin	Chronic bronchopneumonia
21. (S.193)	M	1951	Coughing, vomiting	10 wk.	14 wk.	+	0	+	0	0	Clearing at 17 wk.	1.3	0	64	Penicillin Aureomycin Chloromycetin	Doing well
22. (S.202)	F	1951	Foul stools	2 wk.	5 wk.	+	0	+	0	0	Clearing at 8 wk.	1.5	—	—	Penicillin Aureomycin	Doing fairly well

* Numbers in parentheses refer to series numbers assigned to patients with cystic fibrosis of pancreas in chronologic order of their admission to Babies Hospital.

† All patients received sulfadiazine, penicillin and streptomycin, administered both intramuscularly and by inhalation whenever used.

‡ All patients are receiving either aureomycin or terramycin in prophylactic dosage (25 mg./kg. body weight/24 hr.).

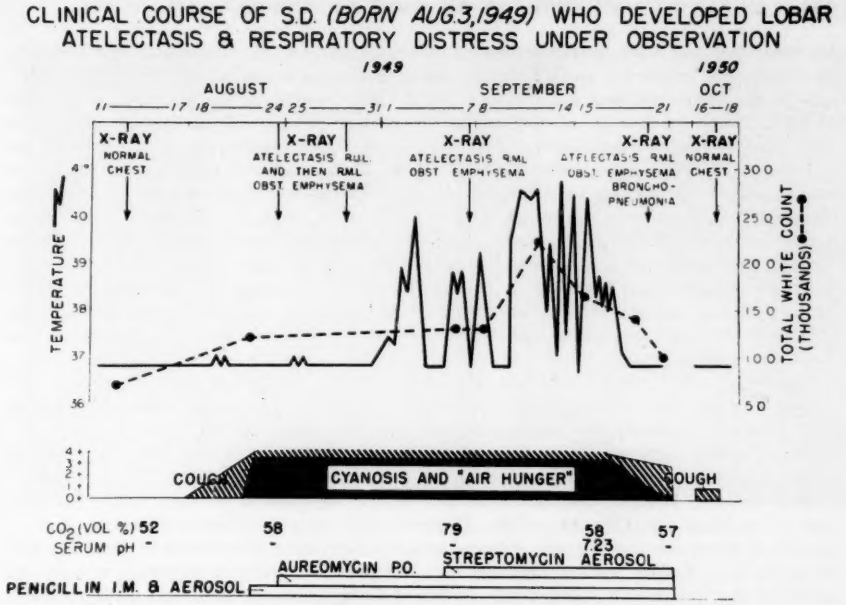

FIG. 1. Clinical course of S. D. (Case 19).

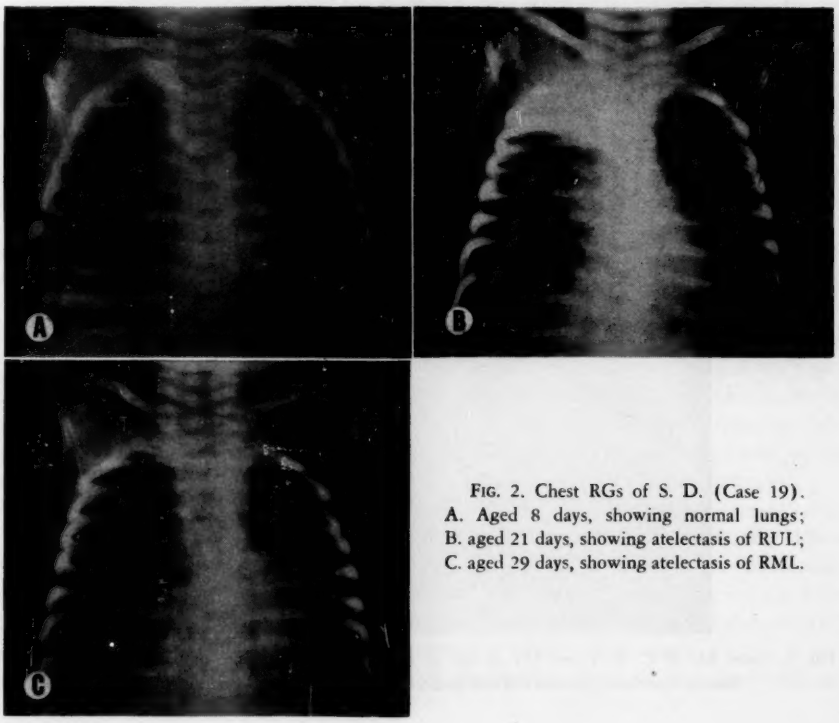

FIG. 2. Chest RGs of S. D. (Case 19). A. Aged 8 days, showing normal lungs; B. aged 21 days, showing atelectasis of RUL; C. aged 29 days, showing atelectasis of RML.

his right chest and acute respiratory distress. A few hours later, his temperature rose rapidly to 40.0°C. He was admitted to another hospital, placed in an oxygen tent and given penicillin. Atelectasis of the whole right lung was recognized by roentgen examination; this persisted until transfer to Babies Hospital 6 days later. On admission, he was found to be acutely ill, dyspneic and cyanotic with physical signs of consolidation of the right lung. Roentgen examination of the chest disclosed atelectasis of the right upper, lower and middle lobes. The mediastinum and heart were shifted far to the right and the left lung was emphysematous (Fig. 3). On fluoroscopic examination, obstructive emphysema was found with surprisingly little exchange of air during the respiratory cycle. Despite oxygen and penicillin therapy and tracheotomy and bronchoscopy, the patient failed to improve and died on the seventh day after admission. The true diagnosis was not suspected clinically and was made only on postmortem demonstration of the typical changes in the pancreas. Besides the atelectasis of the right lung, generalized suppurative bronchitis and tracheitis and multiple lung abscesses were present. Staph. aureus hemolyticus, mannitol and coagulase positive, was grown in pure culture from the lungs and the blood after death.

L.H. (Case 11), a white male infant, was admitted in 1948 at the age of 10 wk. with a chief complaint of coughing and wheezing respirations and failure to gain weight, of 4 wk.' duration. The stools had apparently been normal. On admission, the infant was undernourished and underdeveloped and in slight respiratory distress. There were a few moist rales over the right lower lobe posteriorly, the percussion note was tympanitic and the antero-posterior diameter of the chest was slightly increased. Roentgen examination revealed massive atelectasis of the right middle lobe, best seen in the lateral film (Fig. 4A and B). There was little evidence of bronchopneumonia, and the absence of severe infection was also indicated by a low total and differential white count and sedimentation rate. Various possible diagnoses were considered, including a congenital anomaly and aspiration of a foreign body. Subsequently, because of the appearance of large, foul stools, fibrocystic disease of the pancreas was suspected and then established by the finding of a very low pancreatic

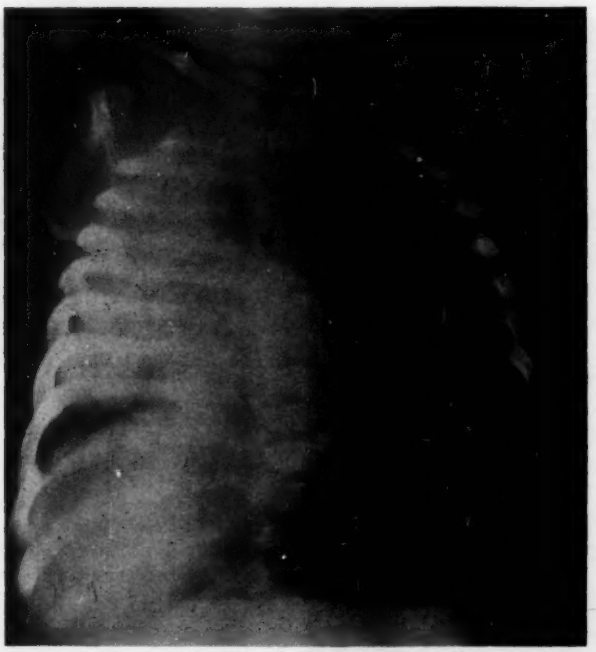

FIG. 3. Chest RG of C. V. (Case 13) at age of 5 mo., showing collapse of whole of R lung. On fluoroscopy there was marked obstruction of L lung and almost no air exchange.

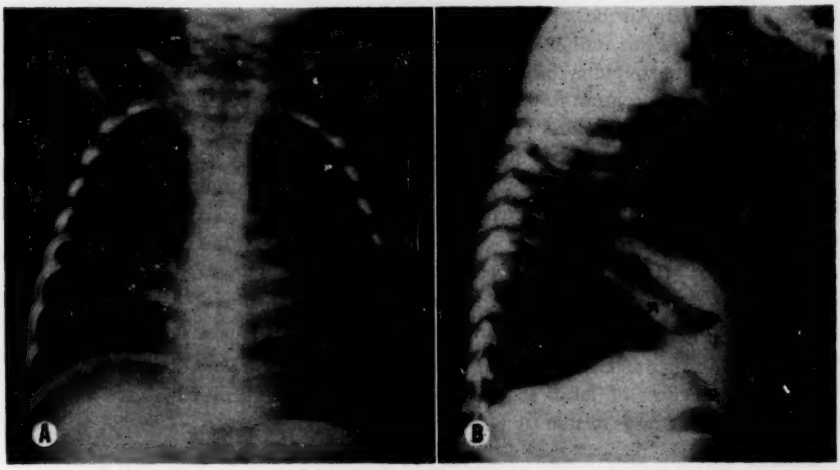

FIG. 4. Chest RGs of L. H. (Case 11) at age of 3½ mo. showing atelectasis of R middle lobe best seen on lateral film.

trypsin. Despite dietary and penicillin therapy, the infant failed rapidly. His respiratory distress increased, the laboratory signs of infection appeared and during the last 7 wk. of his life he required constant oxygen therapy. Throughout, there was no change in the atelectasis of the RML. He died 13 wk. after admission. Necropsy findings included cystic fibrosis of the pancreas, atelectasis of the right middle lobe, generalized suppurative bronchitis and tracheitis, bronchiectasis and multiple abscesses of both lungs. Culture of the lungs yielded Staph. aureus hemolyticus, mannitol and coagulase positive, as the predominant organism, with a few colonies of E. coli.

All patients conformed to the same general clinical pattern, although there were great variations in the duration of single phases. Coughing for several days or several weeks preceded the rapid onset of respiratory distress with cyanosis and "air-hunger," which from then on dominated the clinical picture. After a variable but generally short interval, fever and the usual clinical and laboratory signs of infection, previously absent, made their appearance quite suddenly. After this, the course was that of severe bronchial obstruction with respiratory distress complicated by serious infection.

Fifteen of the 22 patients died (table 1A). The total course of the respiratory illness from the onset of coughing was short in 9 (3 weeks to 5 months), longer in 5 (1 to 3 years). Except for two patients (Cases 1 and 13) in whom a septicemia due to Staph. aureus hemolyticus developed, all died in respiratory failure with widespread bronchial obstruction, anoxia and respiratory acidosis. Right-sided heart failure contributed to the patient's demise only when the total course of the respiratory illness was prolonged.

Of the 7 living patients (table 1B), 4 have developed chronic bronchopneumonia, while in 3, except for occasional coughing, the condition can be considered satisfactory. These 3 patients have been maintained on prophylactic doses of either aureomycin or terramycin. In 6 of the living patients, the atelectasis cleared after varying periods but in Case 16 it persisted almost 6 years despite intensive treatment. The atelectatic lobe was then excised, but pulmonary infection persisted in the remaining lobes of both lungs.

The beneficial effect of combined antibiotic treatment in some cases is clearly demon-

strated in table 1B. All the 7 patients who are living were born after the advent of penicillin. Two received this antibiotic alone initially, the other 5 had aureomycin or terramycin as well. In 5 cases, streptomycin was also given. The value of early diagnosis can also be seen in this table. In contrast to the partial therapeutic success of antibiotics, bronchoscopy was ineffective. This procedure was performed in 7 cases, but in 6 it did not relieve the atelectasis nor save the patients' lives. In the 7th, it seemed to have some measure of success. In 2 infants, both of whom died, tracheotomy was performed in order to permit repeated aspiration of bronchial secretions.

II. Prognostic Importance of Lobar Atelectasis in Cystic Fibrosis of the Pancreas

Comparison of patients with and without lobar collapse suggests that lobar atelectasis is the initiating sign of a severe and at times rapidly fatal respiratory disease (table 1A).

The adverse effect of lobar atelectasis on the prognosis of patients with fibrocystic disease of the pancreas is seen in table 2.

TABLE 2

Effect of Lobar Atelectasis on Prognosis of 194 Patients with Cystic Fibrosis of Pancreas

	No. of Patients							
	Died at Age (yr.)			Total	Living at Age (yr.)			Total
	0–1	1–5	>5		0–1	1–5	>5	
With atelectasis (22 patients)	9	7	1	15 (68%)	2	3	2	8 (32%)
Without atelectasis (172 patients)	22	26	15	63 (37%)	6	54	51	111 (65%)

Statistical comparison of total living and dead with and without atelectasis gives $X^2 = 5.98$, $P = 0.015$

III. Diagnostic Significance of Lobar Atelectasis in the First Year of Life

A survey of the diagnostic files of Babies Hospital indicates that in the period 1939-1951, lobar atelectasis has been entered among the discharge diagnoses, in addition to the basic disease, in 48 infants of less than one year of age. This number includes 10 of the 22 patients discussed in this paper; in the remaining 12, atelectasis was either not included among the final diagnoses or recorded only after the first year of life. Cases of congenital atelectasis were carefully excluded.

An analysis of the 48 cases indicates the following: 10 patients had proved cystic fibrosis of the pancreas; in 10 others a definite diagnosis was not confirmed by duodenal drainage or autopsy, but the clinical picture was consistent with congenital pancreatic deficiency; 9 had either congenital heart disease or intrathoracic vascular anomalies; 3 had amyotonia congenita and the remaining 6 presented a variety of conditions including a case of Kartagener's syndrome and one of probable familial dysautonomia. Lobar atelec-

tasis secondary to aspiration of foreign body or tuberculosis did not occur in infants of less than one year of age.

Further analysis showed that the left lung was affected in 15 cases; in 11 of these, there was no involvement of the right lung. Of these 11 patients, 8 had congenital heart disease or a vascular anomaly, 2 amyotonia congenita and 1 Kartagener's syndrome. Of the four remaining, 3 had acute pulmonary infections, while only 1 of the possible fibrocystic patients had involvement of the left lung.

This survey indicates that cystic fibrosis of the pancreas is an important cause of lobar atelectasis in infancy.

Discussion

It was suggested in 1933 by Wolbach[10] that the fundamental difficulty in fibrocystic disease of the pancreas is the production of an abnormal secretory product by the acinar cells in this organ. This would lead to obstruction of the acini, small and large ducts, by eosinophilic material followed by secondary cyst formation and degeneration of the pancreatic parenchyma. This view has been generally accepted as the explanation for the pancreatic lesions, for the atresia of the gall bladder and for the changes of the liver found in some of these patients.[11]

The relation of the pulmonary involvement to the pancreatic lesions, however, is still a matter for speculation. Two alternative views have been presented: The first suggests that there is a breakdown of normal mechanisms for removal of bronchial secretions owing to failure of intestinal absorption of an essential substance.[11] The second proposes that bronchial secretions are abnormal to begin with and therefore difficult to remove.[7] Arguments for and against each of these hypotheses can be set forth, but it will be noted that whatever the basic difficulty, the result is bronchial obstruction.

Vitamin A deficiency with its consequent metaplasia of bronchial epithelium was thought at first to be mainly responsible for the pulmonary lesions. As pointed out by Andersen in 1946,[11] it became subsequently clear that deficiency of this vitamin may contribute to the changes in the lungs, but cannot be the only or even the main factor involved. The normal serum vitamin A levels in seven patients in the present series and the fact that out of 11 cases that came to postmortem examination, only two had metaplasia of bronchial epithelium (tables 1A and 1B) are further evidence in this sense. However, deficiency of another liposoluble factor or factors essential to normal functioning of the mechanisms for removal of bronchial secretions is not impossible.

According to the second theory,[7] there is in this disease a widespread disturbance of mucus secretion affecting many organs of the body, of which the lesions in the pancreas and the lungs are an expression. Farber, its chief proponent, thus extends to all mucus-secreting structures of the body the concept first put forth by Wolbach to explain the pancreatic lesions. He called the disturbance mucoviscidosis and felt that an autonomic imbalance might be responsible for the altered secretion. The main objection to this theory is that the histologic changes in the pancreas and in the lungs are only occasionally similar; in the great majority of patients they are not. Dilatation of bronchial glands due to apparent inspissation of secretions is only rarely found; in most instances the mucous glands of the trachea and bronchi appear normal or show hypersecretion microscopically similar to that in bronchitis from a variety of causes.[5, 12] Furthermore, the material in the bronchial glands stains as mucus, the material in the pancreas does not.[5]

Neither the hypothesis of a nutritional deficiency, nor the concept of mucoviscidosis, therefore, explains completely the relation between pancreatic and pulmonary lesions. The recent finding[13, 14] of an electrolyte abnormality of sweat-secreting mechanisms in this condition supports the view that cystic fibrosis is a generalized disease, of which the pancreatic and respiratory changes are only one expression. By demonstrating that a glandular system that does not produce mucus is affected, it casts doubt on "mucoviscidosis" as a body-wide disturbance of mucus production. While the significance of this observation is not clear, it opens new avenues for investigation of the basic pathologic mechanism responsible for the protean manifestations of this disease.

Pathogenesis of Pulmonary Lesions: The cycle of events leading to pulmonary involvement is more acute in the case of patients with lobar atelectasis, but is fundamentally the same except in degree for all patients with cystic fibrosis of the pancreas. The following hypothesis is offered in explanation: Because of failure to remove the secretions, acute respiratory infections usually initiate the cycle by causing increased mucus production. Widespread bronchial obstruction results, of which cyanosis, air-hunger and, at times, atelectasis are an expression. After a variable, but usually short period of time, the infection, at first mild and perhaps localized to the main divisions of the bronchi, suddenly becomes widespread and severe by invasion of the obstructed air passages down to their smaller subdivisions. The infected surface is thus suddenly and enormously increased. In the pre-antibiotic era, most patients succumbed at this stage because of spread of the infecting agents to the blood stream. If the patient survives, this cycle can be repeated again on the occasion of subsequent respiratory infections, thus explaining the characteristic course of these children, punctuated as it is by relatively sudden attacks of markedly increased bronchial obstruction and infection. Any one of these episodes may be fatal.

Support for the idea that bronchial obstruction precedes infection of the bronchi comes not only from these observations but also from those of Zuelzer,[15] who reported in 1949 the clinical and autopsy findings of a patient who died as a consequence of severe bronchial obstruction but in whose lungs little or no evidence of infection was found.

Bronchial obstruction may thus be looked on as the primary and cardinal manifestation of the pulmonary component of cystic fibrosis of the pancreas. As a consequence, obstructive emphysema with its severe limitation of respiratory movements, poor alveolar aeration, anoxia and carbon dioxide retention appear. Irregular distribution in the severity of bronchial obstruction leading to poor ventilation of some areas of the lungs contributes to the inadequate oxygen saturation of the arterial blood.

Lobar atelectasis is an expression of severe bronchial obstruction. On the other hand, lobar collapse favors the spread of infection to the involved pulmonary parenchyma, and by resulting in poor aeration of a large segment of lung it greatly contributes to severe anoxia. A vicious circle is thus set up which contributes to the greater severity of symptoms and the malignant course of untreated fibrocystic patients with lobar atelectasis.

Summary and Conclusions

A. Lobar atelectasis with obstructive emphysema occurs in about 10% of patients with cystic fibrosis of the pancreas. In most instances, it appears in early infancy and during the first episode of pulmonary involvement and usually affects one or more lobes of the right lung. It is an indication of severe respiratory disease, whose major expression is widespread obstruction of the bronchi and whose cardinal clinical features are cough, cyanosis and respiratory distress. Rapid onset of bronchial obstruction due to failure to remove secretions

is the initial event; infection is secondary and due to invasion of the obstructed bronchi.

The respiratory disease ushered in by lobar atelectasis represents one of the more severe forms of fibrocystic disease of the pancreas; in many instances it is rapidly fatal unless checked in its progress by the use of antibiotics.

Bronchoscopy and bronchial aspiration through a tracheotomy tube are usually ineffective. Lobectomy is of doubtful value and justified only by the persistence of lobar atelectasis unchanged for a prolonged period. Early diagnosis and early antibiotic therapy are at present the best weapons.

In infants below the age of one year, lobar atelectasis and obstructive emphysema, especially if they occur in white infants and involve the right lung, should suggest the possibility of cystic fibrosis of the pancreas.

B. The pathogenetic mechanism of the pulmonary lesions in cystic fibrosis of the pancreas is more acute and perhaps easier to understand in patients with lobar atelectasis, but is essentially the same except in degree for all patients with this disease. Because of failure to remove the secretions, acute respiratory infections usually initiate the cycle by causing increased mucus production. Widespread and severe bronchial obstruction results and secondary infection of the obstructed air passages follows after a variable but usually short period of time. If the patient survives the first episode, the same cycle can be repeated again on the occasion of a subsequent respiratory infection. Any one of these attacks may be fatal.

Although respiratory involvement is a virtually constant accompaniment of the pancreatic lesions in cystic fibrosis of the pancreas, their interdependence is still unexplained. The two principal theories regarding the interrelationship of the pulmonary and pancreatic lesions of fibrocystic disease are discussed. It is concluded that a satisfactory understanding of this problem has not yet been attained.

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SPANISH ABSTRACT

Obstrucción Bronquial con Atelectasia Lobar y Enfisema en la Fibrosis Quística del Pancreas

Al autor le pareció interesante hacer una revisión y discusión de los fenómenos respiratorios de la fibrosis quística del pancreas, cuya esteatorrea, desnutrición y cambios patológicos en el pancreas que determinan la ausencia de enzimas pancréaticas son relativamente bien comprendidos. Efectivamente, un grado variable de lesiónes bronco-pulmonares es una característica casi constante de la enfermedad, frecuentemente domina el cuadro clínico y determina el futuro del enfermo.

Hizo una revisión de 211 enfermos de fibrosis quística del pancreas y llega a las siguientes conclusiones.

A.-La atelectasia lobar con enfisema obstructivo ocurre en el 10% de los enfermos con fibrosis quística del pancreas. En la mayor parte de los casos aparece en la infancia temprana y durante el primer episodio de manifestación pulmonar, afectàndo usualmente uno o mas lóbulos del pulmón derecho. Es una indicación de enfermedad respiratoria severa cuya expresión mayor es la obstrucción diseminada de los bronquios y cuyas caracterísiticas clínicas cardinales son tos, cianosis y dificultad respiratoria. El fenómena inical es la obstrucción bronquial de principio rápido debido a la imposibilidad de eliminar las secreciones y la infección es secundaria y determinada por invasión bacteriana de los bronquios obstruídos.

La enfermedad respiratoria anunciada por la atelectasia lobar representa una de las formas mas severas de enfermedad fibroquística del pancreas y en muchos casos es rápidamente fatal a menos que se controle su progreso por el uso de antibióticos.

La broncoscopía y la aspiración bronquial a traves de una cánula de traqueotomía generalmente son inefectivas. La lobectomía es de valor dudoso y solo justificada por la persistencia sin mejoría de la atelectasia lobar durante un período prolongado. Las mejores armas en la actualidad son el diagnóstico precoz y la terapéutica antibiótica temprana.

En niños menores de un año de edad, la atelectasis lobar y el enfisema obstructivo, especialmente si ocurren en niños blancos y afectan el pulmón derecho deben sugerir la posibilidad de una fibrosis quistica del pancreas.

B.-El mecanismo patogénico de las lesiones pulmonares de la fibrosis quistica del pancreas es mas agudo y quizás mas facil de comprender en los enfermos con atelectasia lobar, pero excepto en grado, es esencialmente el mismo para todos los enfermos. La obstrucción bronquial con infección secundaria de los bronquios obstruídos es por consiguiente la manifestación cardinal del componente pulmonar de la enfermedad fibroquística del pancreas. Si el paciente sobrevive el primer episodio, el mismo ciclo puede repetirse de nuevo con ocasión de una infección respiratoria subsecuente. Cualquiera da estos episodios puede ser fatal.

Aunque la lesión pulmonar es virtualmente un acompañante constante de las lesiones pancreáticas de la enfermedad fibroquística su interdependencia no está explicada. Ninguna de las dos teorías principales la de la deficiencia nutricional o la de la mucoviscidosis explican por completo la interrelación de las lesiones pulmonares y pancreáticas concluyéndose que aun no se ha logrado un entendimiento satisfactorio del problema.

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ABSORPTION OF VITAMIN A ALDEHYDE BY CHILDREN

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VITAMIN A aldehyde, also termed retenine, is an essential component of the visual process. It can be readily prepared from vitamin A alcohol by various oxidation procedures. Ames et al.[1] have found that when ingested by rats, vitamin A aldehyde is absorbed and converted to a mixture of vitamin A alcohol and its naturally occurring esters. These investigators[1] have also demonstrated that vitamin A aldehyde, like vitamin A acetate, is not toxic in rats unless excessive amounts are administered.

The present investigators were interested in learning if vitamin A aldehyde could also be absorbed and converted into vitamin A by children. If the children were able to accomplish the conversion, they hoped that vitamin A aldehyde would be useful in the diagnosis and treatment of various diseases. The following studies were carried out.

METHODS

The procedure used in the vitamin A absorption tests has been described by McCoord et al.[2]

Solutions in Wesson Oil of all-trans vitamin A as alcohol, acetate ester and aldehyde were prepared by Distillation Products Industries. All solutions contained 63.0 mg. vitamin A alcohol equivalent/cc., which in the case of the acetate is 210,000 U. S. P. U. (United States Pharmacopoeia Units) vitamin A/cc. That is, the solutions of vitamin A alcohol and vitamin A acetate contained 210,000 U. S. P. U. vitamin A/cc., and the solution of vitamin A aldehyde contained 210,000 U. S. P. U. vitamin A activity/cc. In carrying out the vitamin A absorption tests, a basal blood specimen was first obtained and the child was then given by mouth 7000 U. S. P. U. of the form of vitamin A to be tested/kg. body weight. Blood specimens were then obtained 4½ hr., and in the case of some of the older subjects, 7 hr. later. The concentration of vitamin A in the serum of the blood samples was then determined.

Ames et al.[1] did not find any unchanged vitamin A aldehyde in the serum of these subjects after ingestion of the test dose of vitamin A aldehyde.

As there is already considerable information on the absorption of ester and alcohol vitamin A by human subjects, the authors did not attempt to study the absorption of the vitamin A acetate and alcohol in every subject. The aim was to obtain as much data as possible on the absorption of vitamin A aldehyde.

ABSORPTION OF VITAMIN A ALDEHYDE BY NORMAL CHILDREN

The first tests were administered to two normal newborn infants and three older children who were considered to have normal gastrointestinal function. The results obtained are shown in table 1. In the tables, the dashes indicate that no determinations were made at that time. As is shown in table 1, all five children were first given the vitamin A aldehyde absorption test. Two days later the older children BB and CT were given the vitamin A

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* Deceased.

TABLE 1

ABSORPTION OF VITAMIN A ALDEHYDE BY NORMAL CHILDREN

Test dose: 7000 U. S. P. U./kg. body weight vitamin A by mouth

Subject	Sex	Age	Vitamin A aldehyde			Vitamin A alcohol		
			U. S. P. U. vitamin A/100 cc. serum					
			Basal	4½ hr. after dose	7 hr. after dose	Basal	4½ hr. after dose	7 hr. after dose
BS	M	Newborn	53	262	—*	—	—	—
BA	F	Newborn	30	361	—	—	—	—
JD	F	4 wk.	53	1144	—	—	—	—
BB	F	11 yr.	57	521	281	—	942	718
CT	F	12 yr.	160	1980	703	—	2067	726

* The dashes indicate that no determination was made at that time.

alcohol absorption test also. After ingestion of the test dose of vitamin A aldehyde, the increase in concentration of vitamin A in the serum of the children was comparable to the increase found after ingestion of a similar amount of vitamin A acetate or vitamin A alcohol. This is well illustrated by comparing the vitamin A aldehyde and the vitamin A alcohol absorption curves for the child CT.

The increase in concentration of vitamin A in the blood of the newborn infants was not as great as that observed for older children. This difference has previously been noted in the absorption of vitamin A ester and alcohol. However, the authors' experience with the vitamin A absorption test has shown that if the level at 4½ hours is as high as 400 U. S. P. U. vitamin A/100 cc. serum, the absorption of vitamin A by that individual is probably within low normal limits, but not very satisfactory.

Ingested vitamin A aldehyde is therefore readily converted into vitamin A by man as well as by rats.

ABSORPTION OF VITAMIN A ALDEHYDE BY CHILDREN WITH FIBROCYSTIC DISEASE OF THE PANCREAS (MUCOVISCIDOSIS)

The absorption of vitamin A aldehyde by five children with fibrocystic disease of the pancreas was studied and the results are shown in figure 1. The ages of the children ranged from 6 months to 7 years. The presence of the disease was established by the commonly accepted manifestations: the physical appearance of the child (emaciation, pot-belly, poor physical development, etc.); roentgenographic evidence of pathologic changes in the lungs; the absence or abnormally low concentrations of trypsin, amylase and lipase in juice obtained from the duodenum; the fat content of the stools when the child was receiving a normal diet was at least 33% of the dry weight of the stools or 3 gm. or more of fat were excreted per day; relatively flat vitamin A acetate absorption curves and much better absorption of vitamin A alcohol; glucose tolerance curves that were either relatively flat or normal.

In figure 1, the normal absorption curves shown for the vitamin A acetate, the aldehyde

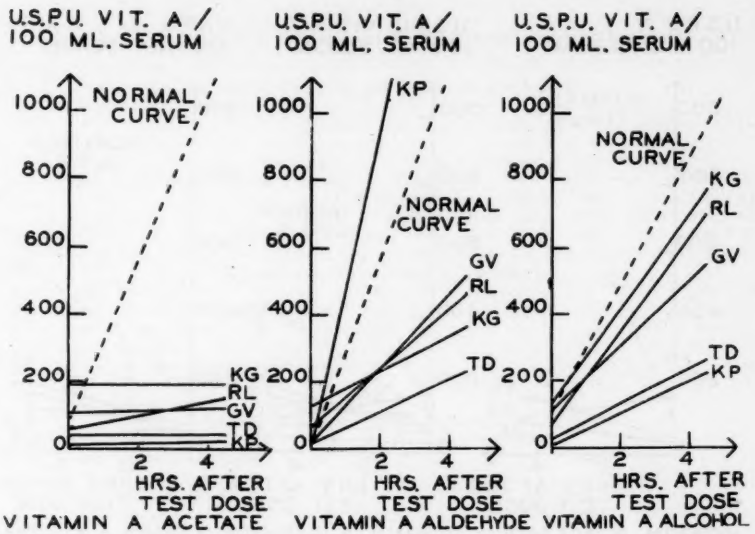

FIG. 1. Absorption of vitamin A by 5 patients with fibrocystic disease of pancreas (KG, RL, GV, TD, KP) compared to absorption of vitamin A by normal children. Oral test dose was 7000 U. S. P. U. vitamin A equivalent/kg. body weight. Patients with fibrocystic disease of pancreas show poor absorption of vitamin A acetate and much better absorption of vitamin A aldehyde and vitamin A alcohol.

and the alcohol represent mean values obtained for the older control children and patients with various diseases who showed no impairment in their absorption of vitamin A. It is evident that children with mucoviscidosis absorbed only small amounts of the vitamin A acetate. On the other hand, they showed much better absorption of vitamin A aldehyde and vitamin A alcohol.

ABSORPTION OF VITAMIN A ALDEHYDE BY CHILDREN WITH CELIAC DISEASE

The series of children with celiac diseases included six subjects whose ages ranged from 2 months to 18 years. The following commonly accepted criteria were used to establish the diagnosis of celiac disease: the physical appearance of the child (emaciation, potbelly, poor physical development, etc.); normal concentrations of trypsin and amylase in juice from the duodenum (lipase was not always found, though this might have been due to the limitations of the method used for its determination); the fat content of the stools when the child was receiving a normal diet was at least 33% of the dry weight of the stool or 3 gm. or more of fat were excreted/day; relatively flat glucose tolerance curves; relatively flat vitamin A acetate and vitamin A alcohol absorption curves.

The vitamin A absorption curves for these patients are shown in figure 2. It is evident, that with the exception of the child RK, the children with celiac disease showed poor absorption of vitamin A acetate, aldehyde and alcohol. RK had been under treatment for celiac disease at the times the second aldehyde and the vitamin A alcohol absorption studies were made.

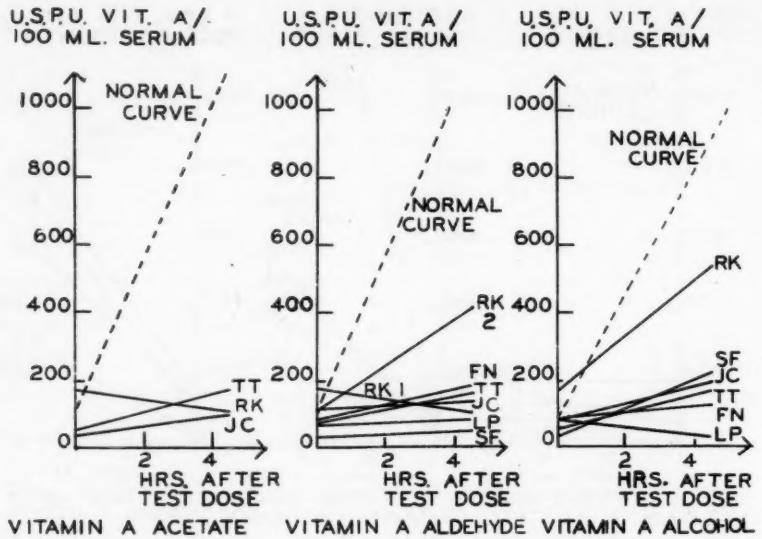

FIG. 2. Absorption of vitamin A by 6 patients with celiac disease (RK, FN, TT, JC, LP, SF) compared to absorption of vitamin A by normal children. Oral test dose was 7000 U. S. P. U. vitamin A equivalent/kg. body weight. Patients with celiac disease show poor absorption of vitamin A acetate, vitamin A aldehyde and vitamin A alcohol.

ABSORPTION OF VITAMIN A ALDEHYDE BY PATIENTS WITH VARIOUS DISEASES

The authors also studied the absorption of vitamin A aldehyde by 27 children and four adults with various other diseases. It is of interest that the majority of these vitamin A absorption tests were requested by members of this hospital staff to aid them in determining whether the patients had fibrocystic disease of the pancreas, celiac disease or some other form of steatorrhea. In these patients, the diagnosis of steatorrhea was finally eliminated by the accepted procedures and criteria: physical examination of the patient; normal fat content of the stools; normal concentrations of enzymes in the juice obtained from the duodenum; consideration of the glucose and vitamin A absorption curves; study of the roentgen films of the lungs and of the gastrointestinal series carried out by the Department of Radiology; subsequent course of the patient during hospitalization.

Table 2 shows the discharge diagnoses and the vitamin A absorption curves for these patients. Those patients in whose serum the concentration of vitamin A was less than 400 U. S. P. U./100 cc. 4½ hours after the test dose of vitamin A aldehyde was administered were considered to have subnormal absorption of the vitamin. When the serum level at 4½ hours was between 400 and 1000 U. S. P. U./100 cc., the patients were classified as showing intermediate or low normal absorption; patients with corresponding levels above 1000 U. S. P. U. demonstrated good normal absorption of vitamin A aldehyde. The absorption of vitamin A aldehyde by the individual patient usually paralleled his absorption of the acetate and the alcohol in cases where the latter tests were administered.

TABLE 2

ABSORPTION OF VITAMIN A ALDEHYDE BY PATIENTS WITH VARIOUS DISEASES

Test dose: 7,000 U. S. P. U./kg. body weight vitamin A by mouth

Patient	Sex	Age	Discharge Diagnosis	Vitamin A aldehyde			Vitamin A acetate			Vitamin A alcohol		
				U. S. P. U. vitamin A/100 cc. serum								
				Basal	4½ hr. after dose	7 hr. after dose	Basal	4½ hr. after dose	7 hr. after dose	Basal	4½ hr. after dose	7 hr. after dose
Subnormal Absorption of Vitamin A Aldehyde												
TG	M	8 mo.	Diarrhea	0	0	—	—	—	—	—	—	—
JW	M	6 yr.	Oxyuriasis of intestine	68	103	—	—	—	—	—	—	—
KG	F	3 mo.	Acute enteritis	53	122	—	—	—	—	76	61	—
TS	M	5 yr.	Giardiasis	27	156	—	—	—	—	—	—	—
VC	F	1½ yr.	Tracheo-esophageal fistula	160	213	—	—	—	—	—	—	—
OM	F	33 yr.	Cyst of bile duct	65	285	741	152	152	289	175	175	452
AF	F	10 days	Gastroenteritis	30	361	—	—	483	—	—	—	—
Intermediate Absorption of Vitamin A Aldehyde												
CH	F	2 yr.	Diarrhea	72	418	—	68	1064	—	—	—	—
AW	F	2 mo.	Gastrointestinal allergy	152	486	—	—	376	—	—	65	—
RZ	M	8 mo.	Fibrosis of myocardium	42	574	—	—	—	—	—	—	—
DP	M	10 yr.	Pituitary dwarfism	61	578	—	—	—	—	—	—	—
DM	M	7 mo.	Diarrhea	106	623	—	—	—	—	—	—	—
RS	F	11 mo.	Congenital heart disease	129	711	—	114	4195	—	—	—	—
MR	F	8 yr.	Diarrhea	125	737	—	—	946	—	—	969	—
BB	M	2 yr.	Horseshoe kidney	53	749	—	110	627	—	—	—	—
BK	M	7 mo.	Diarrhea	118	847	—	—	612	—	—	—	—
GH	M	44 yr.	Laennec's cirrhosis	27	160	1444	114	1775	901	65	844	593
Normal Absorption of Vitamin A Aldehyde												
JM	M	2 yr.	Diarrhea	42	1102	—	—	—	—	—	—	—
RW	M	18 yr.	Asthma	65	1106	1292	—	—	—	—	—	—
RP	M	2 mo.	Congenital megacolon	57	1110	—	—	—	—	—	—	—
LE	F	3 mo.	Infantile cortical hyperostosis	122	1193	—	—	—	—	—	—	—
BK	F	1 yr.	Foreign body in trachea	19	1281	—	—	—	—	—	—	—
HG	M	6 wk.	Central nervous system lesion	171	1284	—	—	—	—	—	—	—
RM	M	4 mo.	Lobar pneumonia	236	1341	—	—	—	—	—	—	—
NW	F	2 yr.	Acute enteritis	34	1360	—	—	—	—	—	—	—
TS	M	6 yr.	Asthma	95	1436	—	—	1425	—	—	—	—
FH	M	78 yr.	? Tuberculosis of lung	198	1919	977	—	—	—	—	—	—
LC	F	6 mo.	Vomiting	65	2018	—	—	1604	—	—	—	—
DW	F	1 yr.	Bronchopneumonia	99	3010	—	—	—	—	122	934	—
JK	F	2 yr.	Bronchopneumonia	91	3530	—	—	—	—	—	—	—
BS	F	7 mo.	Diarrhea	76	4951	—	—	—	—	—	—	—

DISCUSSION OF RESULTS

Inasmuch as vitamin A aldehyde is readily absorbed and converted into vitamin A by persons with normal gastrointestinal function, it is a good source of vitamin A for man.

Children with fibrocystic disease of the pancreas show poor absorption of vitamin A acetate and much better absorption of vitamin A aldehyde and vitamin A alcohol, while children with celiac disease show poor absorption of all three forms of vitamin A. From the results of the studies the authors have been able to carry out, it was felt that vitamin A aldehyde and vitamin A alcohol are about equally well absorbed by children with fibrocystic disease of the pancreas. However, it should be noted that at the present time, vitamin A alcohol is more readily available commercially than is vitamin A aldehyde. Neverthe-

less, the vitamin A aldehyde absorption test is a new aid in establishing the differential diagnoses between muscoviscidosis and celiac disease.

In normal subjects, vitamin A acetate is converted into vitamin A alcohol by the lipase in the small intestine, and the vitamin A alcohol is then readily absorbed through the intestinal wall. The pancreas of the children with mucoviscidosis cannot form the necessary lipase, so these children are unable to absorb much of a test dose of vitamin A acetate, but can absorb vitamin A alcohol well. From these studies, it is concluded that when these children ingest vitamin A aldehyde, they readily convert it in some unknown manner into vitamin A alcohol, which they are able to absorb through the intestinal wall. The authors did not determine the vitamin A partition in the serum after administration of vitamin A aldehyde for they have previously shown that absorbed vitamin A alcohol, even in cases of fibrocystic disease of the pancreas, appears in the serum as the ester.[2]

On the other hand, patients with celiac disease have normal intestinal enzymes, and their inability to absorb vitamin A, fat and carbohydrates in a normal manner is due to some undetermined cause.

Child TS (table 2), who showed subnormal absorption of vitamin A aldehyde, is of especial interest. This child was suffering from giardiasis. It was found that children with giardiasis as well as those with mucoviscidosis assimilate vitamin A alcohol much more readily than vitamin A ester.[2] If further studies show that, in general, patients with giardiasis absorb little vitamin A aldehyde, the vitamin A aldehyde absorption test will be of assistance in establishing the diagnosis of giardiasis.

It is noteworthy that most of the children with gastrointestinal disturbances such as enteritis and diarrhea absorbed the vitamin A preparations better than children suffering from celiac disease. It is hoped that as these studies with vitamin A aldehyde continue, more conditions will be discovered in which the use of this material will be of especial advantage.

Summary

Vitamin A aldehyde is readily absorbed and converted into vitamin A alcohol by the normal human subject. It is therefore a good source of vitamin A for man. Inasmuch as patients with fibrocystic disease of the pancreas show poor absorption of vitamin A acetate and much better absorption of vitamin A aldehyde and vitamin A alcohol, while children with celiac disease show poor absorption of all three forms of vitamin A, the vitamin A aldehyde absorption test is a new aid in establishing the differential diagnosis of these two diseases. The absorption of vitamin A aldehyde by patients with various other diseases usually parallels their absorption of the acetate and the alcohol.

Acknowledgments

The authors wish to express appreciation to Dr. Stanley R. Ames of Distillation Products Industries for his great assistance in carrying out these studies, and to Abbott Laboratories for their aid in the work.

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SPANISH ABSTRACT

Absorción del Aldehido de Vitamina A en los Niños

El aldehido de vitamina A, ó retinina, es un componente esencial del proceso visual, que se prepara por diversos procesos de oxidación de una alcoholatura de vitamina A. Ames y colaboradores encontraron que cuando las ratas lo ingieren, el aldehido de vitamina A se absorbe y convierte en una mezcla de alcoholatura de vitamina A y sus ésteres naturales y que así como el acetato de vitamina A, no les es tóxico a menos que se administre en grandes cantidades.

En nuestros estudios tratamos de ver si en los niños a quienes se les administraba aldehido de vitamina A, éste se absorvía y convertía en vitamina A; se tomaron nuestras de sangre de recién nacidos y niños normales a quienes se les díó por vía oral 7,000 U.S.P. de aldehido de vitamina A por kilo de peso (equivalente a 2.1 miligramos de alcoholatura de vitamina); cuatro horas y media después se obtenían nuevas muestras de sangre. En el suero de éstas las concentraciones de vitamina A fueron mucho mayores que en las primeras, lo que significa que el hombre también puede absorber el aldehido de vitamina A y convertirlo en vitamina A. Nunca se encontró la forma aldehídica de vitamina A en el suero de nuestros sujetos después de la ingestión de la dosis de prueba de aldehido.

En los niños con enfermedad fibroquística del páncreas que mostraron poca absorción del acetato de vitamina A, se vió mucho mejor absorción del aldehido y de la alcoholatura de vitamina A; los niños con enfermedad celiaca mostraron absorción muy deficiente de las tres formas de vitamina A. La prueba de absorción del aldehido de vitamina A se considera como una nueva aquda en el diagnóstico diferencial de estos dos padecimientos.

Enfermos con otros padecimientos mostraron igual capacidad para absorber el aldehido de vitamina A y convertirlo en vitamina A, que para absorber el acetato y la alcoholatura de vitamina A.

260 Crittenden Boulevard

Pediatrics

VOLUME 12 AUGUST 1953 NUMBER 2

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

COMMITTEE ON ACCIDENT PREVENTION

The Committee on Accident Prevention has submitted the following statement:

PRECAUTIONS IN THE USE OF FLUOROSCOPY

GENERAL

No unnecessary examination should be made.

A history of any previous x-ray exposures—by fluoroscopy or roentgenography—should be obtained.

Carry out at no more than 3, but preferably 2 milliamperes.

Record the durations of each examination and the site examined on the child's history.

EQUIPMENT

Filters 2-3 mm. aluminum are to be used.

The longest possible target—table top distance—preferably 18" should be used.

Calibration of output (r) of machine should be made not less than once a year unless the tube has been changed or other repairs made.

Machines should have a timing switch which cuts off automatically after 5 minutes.

The machine and controls should be of shockproof type.

METHOD

Accommodate before fluoroscopy (use red glasses—10 minutes before entering fluoroscopy room).

Wear protective apron and gloves.

Use the *minimal* field compatible with the requirements of the examination.

Never increase milliampere settings to "see better."

COMMITTEE ON TUMOR REGISTRY
COMMITTEE ON ACCIDENT PREVENTION

Pediatrics

VOLUME 12 AUGUST 1953 NUMBER 2

SPECIAL SECTIONS

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

A RESEARCH PROGRAM FOR THE CHILDREN'S BUREAU

A PUBLICATION from the Children's Bureau under the authorship of Helen Witmer, Ph.D., now Director of the Division of Research, reviews the past research program of the Children's Bureau and offers proposals for the further development of this program. The author first outlines the Bureau's past research work originating with the Act of 1912 which created the Bureau and which stated that the Bureau "shall investigate and report . . . upon all matters pertaining to the welfare of children and child life among all classes of our people." From this historical perspective, proposals are then made for the future research program of the Bureau.

Those who are interested in the implications of the Bureau's past studies in relation to future research will find them well described by Dr. Witmer. For the purposes of this column, we are more interested in current and future trends. The following are excerpts from this bulletin directed to the question: where do we go from here in the research program of the Children's Bureau?

In conducting investigations the Children's Bureau has two main objectives. First, it aims to assemble the facts needed to fulfill its obligation to keep the country informed about matters that adversely affect the welfare of children. Secondly, it aims to determine what kind of health and welfare measures and methods are most effective in aiding children and their parents. The first aim derives from the basic Act establishing the Children's Bureau; the second is a necessary concomitant of the Bureau's responsibilities under Title V of the Social Security Act. The two aims, obviously, are closely related. The carrying on of programs requires information about needs. Vice versa, having secured the facts about the handicaps under which numerous children live, we naturally want to know by what means they can be diminished. Together these aims provide the basis for an integrated research program.

These being the objectives, it follows that the Children's Bureau research plan is chiefly concerned with answering practical questions about the well-being of children rather than with carrying on basic research, and that any theoretical investigations that are conducted will be undertaken with a practical end in view. Accordingly, the plan starts with common sense surveys of conditions affecting children adversely, goes on to questions that grow out of the every-day practice of health and welfare agencies, includes applied research in the usual sense of the word, and contemplates theoretical investigations being undertaken when lack of scientific knowledge clearly handicaps understanding and practice.

Handicapping Situations and Conditions

Surveys of situations adversely affecting significant groups of children is the kind of investigation frequently carried on by the Children's Bureau during its early years. It represents the literal carrying out of the Bureau's mandate to investigate and inform the public about matters bearing on the welfare of children. The situations to be studied would be, for the most part, those that had already aroused public concern. The questions to be answered are whether the situation is disadvantageous to children and what it consists of, how widespread it is, under what conditions it arises, what it entails for children, and what is being or might be done about it. Current examples of situations of this kind are: "black markets" in babies, employment of mothers of young children, migrant labor, and other situations of very low income, etc.

In addition to easily identifiable groups of children whose welfare is threatened by grossly unfavorable situations that probably require broad social and economic action, there are many children whose disabilities are of a more individual character, many of whom must be brought to the attention of service agencies if they are to function adequately. Among these are the physically or intellectually handicapped children, juvenile delinquents, and those likely to become delinquent, children who are homeless or neglected or whose parents are otherwise in need of assistance in regard to family matters, and so on.

In the health field there is, for example, much interest in mass screening methods. In some areas, valid devices are available for detecting early signs of disease and malfunctioning; in others, the methods currently available are too crude to be very useful. In the social field also there is interest in early identification of disorders, especially with respect to children "in danger of becoming delinquent" or of developing other personality and behavior disorders. In both fields it is not only a matter of prediction of future disorders. Also involved is the identification of children already handicapped physically, intellectually or socially. Such information is needed not only as a basis for determining the size and character of the service programs required and for judging the extent to which present programs are meeting the need but also as a source of control data for determining both the efficacy of programs and the conditions under which outside aid is not required.

Programs and Methods of Service

Having identified particular categories of children in need of individual assistance, the next question is, what is the nature of their needs. This question will, of course, have to be explored for each group separately. The point at issue here is not the exact methods to be used by the various professional and non-professional persons concerned but the

aspects of the children's lives to which attention will have to be paid if the children are to be adequately served. What services do the children and their parents need? What problems are encountered in supplying such services? To what extent do needs for, desire for, and ability to use services coincide? What are the distinguishing characteristics of the kinds of cases in which offered services are rejected? What happens to the children who do not receive aid thought to be needed? What are the distinguishing characteristics of the children and their circumstances in cases of this kind that work out reasonably well?

Analysis of present service programs might be made either of individual programs or agencies or of all programs in a certain field in, say, a city, county, or state. It refers to these programs' objectives, clientele, expense and coverage, administrative problems, and effectiveness. Among the programs to be studied are those which serve children who are homeless, temporarily or permanently, or neglected, or whose parents want help with problems of child-rearing; those for unmarried mothers and illegitimate children; those for delinquents and children "in danger of becoming delinquent"; those that serve children who are crippled and those devoted to advancing maternal and child health, and so on.

Within present programs there is much variation in measures and methods used and much debate about which are preferable and for what reasons. Much of the argument, in the social welfare field particularly, centers around application of theory, and there has been little appeal to fact for confirmation. In some areas, even the exact nature of the treatment method is unclear, and it is not even certain that terms are being used consistently or with the same meaning to all concerned. This being the case, it is not surprising that differentials have not been determined at all adequately and that there is little knowledge about what methods and measures are most effective in specified types of cases.

Although measures are designed to help children who are in one or another kind of difficulty, it often happens that the measure is concerned with the particular difficulty under consideration and may have unpremeditated effect on the child as a whole and on his family life. For example, under certain conditions hospital care may be thought necessary for pre-school children, severely handicapped children may be thought to require the kind of training only an initiation usually affords. Do the supposedly needed measures have detrimental side effects? What can be done to reduce or overcome them?

The Children's Bureau's concern with the welfare of children is not limited to the discovery of disadvantageous situations and of the means by which handicapped children may be aided. The Bureau also seeks to learn the causes of these situations and how the development of difficulties in children may be prevented. The assumption back of most preventive measures is that the condition will develop in a significant proportion of cases under certain specified circumstances. Preventive measures are aimed at removing or modifying these adverse circumstances, and instituting correctives, or at supplying compensations. This requires the prior identification of the associated factors. There is needed, too, a progressive pushing back along the line of inquiry to discover the conditions under which these associated factors develop or merge. In such a search, projects aimed at prevention, if carefully designed and carried out, can serve as experimental situations in which to test the validity of the hypotheses regarding causation.

In addition to studying what is now going on in the field of services for children the

Bureau would perform a very useful service in bringing to the attention of professional workers theories and facts from the behavioral disciplines that have not yet been taken account of in their practice. Studies of this sort would range from those that reviewed and analyzed findings in a particular area and raised questions for the professions to those that attempted to work out the logical implications of a body of theory for certain aspects of the practice of a particular profession. In connection with these studies, pilot studies might be set up to test the value of the findings for work with children. Reviews of this sort should also cut across disciplines in order to indicate what various disciplines have to say on specific topics. Out of such reviews, even more than out of those based on single disciplines, questions for further research would arise, many of which would be of a practical nature.

Basic Facts and Theories

Many of the subjects proposed for study above lead directly or indirectly into unresolved theoretical issues, as well as into questions on which factual knowledge is lacking. A sharp line cannot be drawn between the studies of a theoretical nature and the practical investigations suggested above. A distinction can be made, however, between research that starts from a theoretical question and that which arises out of the problems of practice. It is the latter, according to this plan, that the Children's Bureau would be chiefly concerned with. Just what the range of theoretical investigations would be cannot be stated in advance, since the investigations would not be the outcome of systematic explorations of fields of science but would rather develop as lack of knowledge was disclosed in the source of practical studies. The following, however, are examples of such investigations in areas in which lack of knowledge handicaps practice: values and customs of sub-cultures in the United States with special reference to their bearing on health and welfare matters; essential elements in constructive behavior and attitude change; individual differences among children, especially those of a congenital character; importance for children of parental affection and continuity of care by own parents; effects of economic privation on children's physical and emotional health, on the emergence of latent capacities, on the ability to function in American society; effects of prejudice and discrimination on children's development and utilization of capacities.

How the Research Might Be Carried On

If this is to be the scope of Children's Bureau research interest, how can the Bureau operate so as to further the increase in knowledge in these areas? Before that question can be adequately considered, certain peculiarities of the situation with respect to these areas must be described.

For the most part, these are areas in which very little research is currently being carried on or ever has been carried on under any auspices. Even fact-finding investigations have been scarce, the early Children's Bureau investigations notwithstanding. This is particularly true of the welfare field, but in the health field, too, few of the questions proposed above have been adequately answered, especially those that relate to the social and emotional aspects of children's difficulties and the measures used to deal with them. In both health and welfare fields, little attention has been paid to the explicit application of the concepts and viewpoints of the behavioral sciences and to testing their usefulness for practice.

This being so, it follows that methods appropriate to the answering of the kinds of

questions proposed for investigation have not yet been adequately developed. In addition, the number of research workers competent to deal with these questions is small, for what is required for the best work is both knowledge of scientific theory and technique and clinical experience in the field under consideration or at least clear understanding of the field's problems. Accordingly, in undertaking to carry on or to promote research along the lines proposed above, the Children's Bureau, for the most part, would be breaking new ground with respect to subject matter and to some extent, with respect to method. It would not be duplicating the work of other governmental agencies or private organizations, though, of course, in many particular investigations their cooperation would be needed.

Governmental agencies characteristically operate in the research field in one or more of three ways. They may carry on research on their own, in laboratories or field stations under their own management or in cooperation with others. They may contract with universities and research organizations to do the work, the subjects for research being proposed either by themselves or by the contracting agency. They may provide grants to individuals or organizations to pursue studies of their own planning.

Because of the nature of the subject matter to be dealt with, the first of these means is open to the Children's Bureau in only a limited kind of way. Most of the questions on which answers are sought are those that concern children and their families in particular social, economic, and cultural circumstances. They are not questions that can be studied in a laboratory or institute set up at headquarters. To answer them one must go to the field, seek out the subjects of study, and work with those who provide services.

For many of its studies, therefore, the Bureau would need itinerant research teams or would have to station research workers in appropriate places or otherwise carry on research where the opportunities were presented. In such carrying on of studies away from home base the Bureau has had much experience. The advantages and the difficulties thus revealed should be carefully examined for their implications for future studies.

The other two devices commonly used by governmental agencies for furthering research —contracting for research to be done by others and subsidizing research proposed by others—would be of limited feasibility for the Children's Bureau at present, even if they were permitted by law. The reason for this lies in the small number of research workers who are equipped by training and experience to work on these problems. The knowledge and skills required cut across university departments and professional schools, and there are few research organizations working in the areas of the proposed research.

The most likely sources of interest in undertaking this kind of research are welfare agencies, public health programs, hospitals, and the like, though the various professional schools are also possibilities. In most of these organizations research personnel of the needed kind are scarce. Social agency research workers are likely to be narrowly statistical in their training and interests and are unlikely to have the broad theoretical viewpoint that is desired. Those in the health field are for the most part laboratory scientists or specialists in vital statistics. The individuals who are most likely to be interested in the analysis of qualitative data are largely lacking in research know-how.

If, then, none of the usual devices for further research through governmental agencies seem adequate to the task at hand, what other means are to be considered? Some possibilities are suggested by the very nature of the difficulties that have been described. It has been implied that one of the chief problems in carrying on research of the desired

kind is to effect a union between the ideas, observations, and questions of those who are close to actual practice and the viewpoints and technical know-how of those who are expert in research on theoretical issues. Both individuals and research organizations that have this special competence are few. If the Children's Bureau, in carrying on its research activities, could operate in such a way as to promote this mutual understanding and also increase the supply of research workers, it would be achieving a double purpose. The following proposals are made with this objective, as well as that of promoting research, in mind: the Bureau might: (1) take as one if its chief functions serving as a liaison between theorists, research workers in the health and welfare fields, and practitioners at various administrative levels; (2) provide consultation services to agencies and organizations wanting assistance in carrying on practical studies within the scope of the Bureau's interests; (3) aid states in undertaking studies financed by grant-in-aid funds; (4) carry on certain projects on its own or in cooperation with other federal agencies. For these studies, particularly the latter, the Bureau could utilize the advice of its own multi-discipline staff for planning, enlist the help of universities for advice and provision of research assistants, and discuss methods and findings with advisory committees drawn from the various professions and disciplines. For any of this work, considerable expansion of staff and funds will be necessary. In this connection, the Bureau might consider providing research internships for graduate students and recent graduates in the behavioral disciplines and professions. By this means the supply of competent research workers would be directly increased, and the Bureau would benefit immediately and in the long run.

Specific Areas for Study in the Near Future

Planning research for the Children's Bureau requires also that suggestions be made about areas in which the Bureau should immediately or in the near future undertake to carry on studies. Accordingly, the following list of subject areas is presented: (1) evaluation of current child health and welfare programs and measures and methods of determining their effectiveness; (2) effects on children of separation from their parents; (3) cultural norms and values as factors influencing parents' and children's response to health and welfare measures; (4) means of effecting change in the attitudes and behavior of adults in matters affecting children; (5) types of delinquents, effective methods of preventing delinquency and treating delinquents; (6) effects of economic privation on the health and development of children, on the emergence of their latent capacities, on their ability to function in American society; (7) infant mortality and morbidity.

In these proposals in regard to investigations to be entered upon in the near future, the guiding consideration has been to suggest topics that cut across many programs and activities in the fields of child health and welfare and that have both theoretical and practical implications. Successful studies in most of the areas listed above should result in new knowledge that would be widely applicable, as well as contribute to the solution of problems of immediate concern to health and welfare workers.

This proposed program for research by the Children's Bureau is one that, it seems to us, is not only in line with the Bureau's tradition but also much needed today. The area indicated by those questions is largely an untilled field so far as scientific research is concerned. Relatively speaking, little money and little research talent is being employed or ever has been employed by the Federal or State governments or by private research

organizations in undertaking to discover the answers to the kinds of questions posed above.

There has been little scientific research in regard to either social services or the social aspects of public health. In both the social service and the public health fields, however, there is growing interest in applying scientific method to the collection and analysis of social data for the purpose of determining the effectiveness of programs and of testing the hypotheses on which programs for children are or might be based. So far, however, little of scientific worth has been accomplished, and even the methodology of investigations is poorly developed.

As to the analysis of social and economic conditions inimical to children's well-being, the present research situation is even less encouraging. No research organization of any magnitude has taken this as its field of interest. The few studies that have been carried on—aside from those of the Children's Bureau in its early days—have been sporadic investigations, such as the occasional ones dealing with the plight of migrant children; and there is no concerted effort on the part of any research group to get the facts and to develop or synthesize the theory relevant to such matters. In view of our present knowledge of how important the environment and experiences of childhood are for the full development of human beings' potentialities and in view of the country's need for healthy, creative, loyal citizens, it is surprising that this is so. The Children's Bureau, of course, cannot take on this whole job. Given funds and a creative staff, it can however, provide leadership in this area and can play an important part in mobilizing scientific effort in this regard.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

IT IS almost a truism to say that solution of any medical or public health problem frequently brings to light other, often unexpected, corollary or subsidiary problems. Increased recent interest in the public health approach to prematurity, stimulated by its growing relative importance as a preventable factor in infant mortality, has resulted in many effective city and state programs. The one in New York City has been of particular interest because of the general wealth of the city's medical resources. It is no surprise that the problem described in the following article came to light but it is heartening and edifying to note the concerted and effective approach used in meeting the new development.

A COMMUNITY PLANS FOR AFTERCARE OF ITS PREMATURE INFANTS

By HELEN M. WALLACE, M.D., MARGARET A. LOSTY, R.N., AND MILDRED E. HEARSEY*

THE city-wide program for prematurely born infants administered by the New York City Department of Health has brought into prominence the problem of community placement when the premature centers are unable to discharge infants directly home, for various reasons. This problem has existed to some extent for years but the concentration of infants in premature centers has focused more attention on the necessity of community planning and action.

POLICY OF HOSPITAL DISCHARGE AND REASONS FOR INABILITY TO DISCHARGE CERTAIN PREMATURE INFANTS

On July 1, 1950, a broad program aimed at improving the care of premature infants was initiated by the City Health Department, including payment for hospital care of certain premature infants in approved premature centers at a rate of $12 per diem. One of the policies established stipulated that payment at the $12 daily rate would automatically cease when the infant reached 5½ pounds unless there was a medical reason for continuing hospitalization in the premature center. Several undesirable practices thereupon came to light: (1) Premature infants who reached 5½ pounds and who no longer needed the highly specialized pediatric and nursing care, had, in fact, been kept in the centers, thus depriving smaller premature infants of such care; (2) On the other hand, in order to avoid this difficulty, at times, infants were being transferred to the general pediatric service of the hospital, thus exposing them to the dangers of cross-infection prevalent on the service, or were being discharged to homes unsuitable (a) from a physical standpoint, because of the presence of infection in the home, lack of equipment, or inadequate

* From the New York City Department of Health.

housing, or (b) from a social standpoint, because of the presence of illness or complex family problems.

These problems were called to the attention of the Department of Health by the pediatricians-in-charge, supervising nurses, and medical social workers of the premature centers soon after the first centers were developed. They were concerned by the two-fold problem, that failure to insist on discharge at 5½ pounds resulted in limitation of use of the beds provided in the center, and that insistence on the rule created hazards for some babies through forced placement on the general pediatric service or in unsuitable homes, possibly negating the value of the skilled care previously provided.

Steps Taken in Community Planning

Conferences with the pediatricians-in-charge, supervising nurses, and medical social workers of the premature centers, with Health Department personnel as coordinators, resulted in the following steps:

The first step was to strengthen the existing home follow-up program carried on by public health nurses. It was emphasized that the early referral to public health nursing agencies, recommended in the basic plan, was essential if time were to be allowed for proper planning. It was suggested that the first referral should come as soon as it was known that the infant would survive and certainly no later than when the mother was discharged from the hospital. This step meant where there were home problems, efforts to eradicate or ameliorate them were made earlier.

The second step was to promote fuller use of other services available from the Department of Health and the Department of Welfare, to meet such situations as lack of heat, unsanitary home conditions or lack of equipment at home. In the Health Department, for example, under the rat control program, the homes of premature infants were given priority. In the Department of Welfare, policies and procedures of obtaining aid were made more effective and clearer to the Department of Welfare field staff, the public health nurses, and the premature center staff. Lack of equipment was found principally in homes of Department of Welfare clients. This situation was partly due to inadequate information regarding provisions included under "Public Assistance" and "Home Relief," and partly to lack of procedures to insure prompt service. A conference with representatives of the Department of Welfare resulted in the facilitation of funds for the purchase of home equipment for premature infants in welfare families. Information circulars were sent to the personnel of public health nursing agencies and medical, nursing and social work staffs of the premature centers regarding the type and amount of equipment which could be provided by the Department of Welfare. The teaching program for parents in the premature centers and the visits by public health nurses to the homes both played a role in assisting the parents in the selection of home equipment necessary for the care of their infant.

An additional step was to develop a program of placement in foster homes for those babies who for social reasons could not be discharged to their own homes. The Health Department initiated several meetings with varied professional representatives of the Welfare Department's Child Welfare Division, of the Department of Hospitals, of voluntary child caring agencies concerned with the problem, and of the premature centers. It was learned that most of the agencies could not accept an infant weighing 5½ pounds but a voluntary child placing agency had for years provided convalescent care in foster homes for mildly ill and young children who were temporarily unable to be cared for in

their own homes. Officials of this society became extremely interested in the problem of the premature infant and offered the facilities of one of their foster home units for infants weighing 5½ pounds.

Such infants are placed in this foster home unit for a maximum of three months' convalescent care. A rate of $4 per day is paid by the Division of Charitable Institutions of the Department of Hospitals for those who are medically indigent. Ability of a family to pay for care is determined by the referring premature center, and payment is expected to the extent possible according to a family Budget Guide set up by the Department of Health. The three months period of foster home care on a convalescent basis allows opportunity (1) for the simpler social problems to be solved so that the baby may return home safely; and (2) for social agencies to make and implement a long range plan for the temporary or permanent placement of dependent children who cannot return home. If this program works well, it is hoped that other child-caring agencies will make available, either on a "convalescent" basis or foster home basis or both, needed care for those infants who reach a weight of 5½ pounds.

Summary

Long standing problems of over-hospitalization and inappropriate hospital discharge of newborn infants have been brought to attention by the concentration of premature infants in centers, through the interest of pediatricians, nurses and social service staffs at these centers. A plan for improved after-care was made and put into effect through joint community effort of health, welfare, and social agencies concerned. This plan consisted of: (1) strengthening of the existing home follow-up program; (2) promoting fuller use of other services available from the Health and Welfare Departments; (3) developing a special program for placement in foster homes.

EDUCATION

GROVER F. POWERS, M.D., *Contributing Editor*

SOME OBSERVATIONS ON PEDIATRIC EDUCATION

CAN you tell me, Socrates, whether virtue is acquired by teaching or by practice; and if neither by teaching nor by practice, then whether it comes to man by nature, or in what other way." At the conclusion of the dialogue Socrates gives an answer: ". . . virtue comes to the virtuous by the gift of God. But we shall never know the certain truth until, before asking how virtue is given, we inquire into the actual nature of virtue."

In the Great Didactic of Comenius is this precept: "Let the main objective . . . be as follows; To seek and find a method of instruction, by which teachers may teach less, but learners may learn more."

Ralph Waldo Emerson said: "That which we are, we shall teach, not voluntarily but involuntarily."

Abraham Flexner observes that "There are men who teach best by not teaching at all."

These quotations will be interpreted by you each in his own way; to me they penetrate into the heart of sound educational philosophy. If each of us would realize that great teaching is by great practice, and practice is the medium through which example is set, and example is the tool by which excellence may be demonstrated, and happily, if conbined with experience, learned, then we would not ignore but cease to stress heavily the concepts apprehended by such terms as "full time," "part time," "private practice," "didactic lectures," "audio-visual aids," "decentralized teaching," "workshops," "teaching and nonteaching hospitals," etc. We would appreciate rather, that all of us who practice medicine teach—involuntarily always, voluntarily sometimes! We set examples and somebody is always watching, somebody is always listening! Dr. Gregg calls our attention to an appropriate comment in a Portuguese language textbook: 'Language is of three kinds; first spoken, second written and third gesticulated."

There can be no fundamental schism between "practitioner" and "professor"; both profess medicine, set examples thereby and thus teach. Of all groups in medicine have not pediatricians the most important students—babies, children, parents, nurses, interns, residents, social workers, school teachers and others concerned with child health!

In the academic area I know of no department of pediatrics which does or could or desires to function without the support and participation of those who serve with little or no financial remuneration—"part-time." The extent and quality of their teaching, as with everyone's, is dependent on the teacher and not on the system under which he functions. No administrative officer minimizes the unique and specialized contribution which the teacher who spends much of his time in private practice can bring to the eager mind of youth; and the practitioner, in turn, receives as his chief reward stimuli and inspiration from his students. But there must be dependability in meeting assignments and responsibilities and no casual repetition of clinical platitudes which fail to conceal devastating ignorance of advances in knowledge in medicine.

Read before the Committee on Medical Education at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 21, 1952.

From the perspective of over 40 years, I realize now that my greatest teacher in medical school was William Stewart Halsted, Professor of Surgery in the Johns Hopkins University. At the time, I thought of him not as our most popular teacher but rather as our most ineffective professor. He could not verbalize well in a lecture; he was not authoritative; he probably did not use lantern slides skillfully; at his clinics, even if I sat in the front row, I could hear only a portion of his comment although I could always observe his gentle, respectful manner with patients, students, and staff; on ward rounds I could hear even less and saw but little; at operative clinics, one sensed infinite care and striving for perfection but I neither heard nor saw anything which then seemed important. Or did I! For somehow, in some way, over the course of the years I have come to realize in a personal way that Halsted was a truly great doctor and teacher; a humanitarian in dealing with his patients; a scientist in his quest for truth; a scholar in the depth and scope of his learning; a physician I would fain emulate. "What we are, we shall teach"; "men who teach best by not teaching at all"! "Halsted men" staffed many of the surgical clinics of this country; and is there a better measure of the greatness of a teacher? Dr. Alan Gregg has well said: "What Welch and his colleagues (Halsted, Osler, Kelly) did and believed and wrote is not as important now—nor anywhere near as important—as the heritage of excellence their contacts with each other have left us."

Because I fell so deeply the fundamental importance of the power and effectiveness of teaching by the example of fine practice, I am concerned at what is happening in many clinical departments in medical schools. I was an intern when "full time" was born in Baltimore; that educational infant was so christened not primarily because more skill was thought to be needed in medical education, but because there was demand for greater concentration of time, effort and energy on clinical services and in laboratories. And the chief concern for the success of the new program was that full time doctors might lose their "clinical touch" since they were to have little private practice and were to devote the time and effort formerly so expended to investigative work. For the most part, however, full time men have not deteriorated clinically but rather advanced, and this usually at the expense of time and effort which were to have been spent in the laboratory. But in recent years a menace to the clinical teacher has come from another quarter—administrative responsibilities, fund raising and public service; these seriously threaten excellence in education in pediatrics and in all or most clinical fields. This menace has been well-described by Dr. Harry Gordon in a letter addressed to the Chairman (Dr. Hill) of this Academy Committee. Gordon says: "A serious threat to the efficiency of the professor has come from demands on him for more obvious services to the community, as though the more traditional role of a university professor does not constitute such service. The reasons for these demands are clear: the last war with its awful recognition that 'the bell tolls' for all of us, the extent of the World War II mobilization for direct service to the government either on a civilian or military basis, the continuing partial mobilization of the cold war, the extensive governmental support of research and health programs, the great extension of post-graduate medical education stimulated originally by the need of refresher courses for doctors discharged from the military service, the improvement of air transport, have all led to the assumption of responsibilities outside the university on an apparently unending basis by professors. The full-time professor is forced to become less than a part-time visitor in his own department, less because it is assumed that he is discharging responsibilities which in fact he

is not, and this would become obvious quickly were it not for the loyalty of colleagues. His junior attending and resident do not bother him about individual patients, because he is too busy with administrative emergencies, and his rounds are held irregularly because national committee meetings take precedence. In truth, the man who is supposed to teach direct health services mostly by the precept of giving them has become a lecturer whose words carry their greatest weight at points far removed from the site which should occupy his major energies, namely, his own department.

"The very goodness of the demands by the community markedly increases their centrifugal power and also makes it difficult to avoid meeting them without having it appear that one is for sin. Rev. Harry Emerson Fosdick has written that one of the most difficult decisions in life is to choose between two good goals; perhaps your committee could help clinical teachers to the choice of work in their departments as their primary responsibility."

Gordon wrote primarily of this threat of engrossing administrative and public service to the full time chiefs of medical school departments, but it applies to all physicians since we are all teachers in our practice and so exemplify our science and our art. To the degree we assume other responsibilities—for which worthy openings are continually being presented—the integrity and the quality of our medical teaching is being jeopardized, of this we must be on guard.

Since January first, 1952, the Committee on Education has sponsored meetings of academic teachers and academy State Chairmen at teaching hospitals in 9 of the 10 areas into which the U.S.A. and Canada are divided; I had the pleasure and honor of attending 8 of these conferences. The most important achievement of the meetings, it seems to me, is the stimulation and inspiration which comes to earnest people when they come together in a small group and discuss their problems, their failures, their accomplishments, their plans, their ideals. In most of the conferences, discussion was developed in the framework of the actual educational program of the host department presented in many instances by students and junior staff members whose interest and participation was most rewarding. There are many interesting facets of these conferences which might be brought to your attention relating to what aspects of pediatrics should be taught (content, i.e., fluid balance, growth and development, infectious diseases, prematurity, etc.); how the teaching should be done (methodology, including research as a pedagogic instrument)* where, in any given environment, the teaching program should be located (inpatient, outpatient, affiliated institutions, child health conferences, nursery schools, etc.); when in the medical course students, graduate and undergraduate, should be exposed to various aspects of the subjects (curriculum); and who should teach and be taught and for how long (faculty). At this time I shall focus attention upon three areas of discussion making the introductory observation that most departments have as much curricular time allocated to them as they have staff and programs to utilize effectively. This situation is due in all probability to the impact on medical school administration of the Academy Study of 1946. There are still departments, however, in which expansion is desired in allocated pediatric hours as well as in facilities and resources.

Pediatrics and the rotating internship in the first subject I wish to stress. I have always advocated and still do the "straight" internship of high quality as the most vital and

* I know of nothing which brings student and teacher so close together mentally and spiritually as joint endeavor directed toward the solution of a problem.

rewarding educational experience a young graduate in medicine can have when taken the year immediately after receiving his degree. There is then an open mind and few fixed habits of practice; instead, there is flexibility and vivid enthusiasm and interest runs high; the emphasis is not on content so much as on quality; not on "qualifications for the practice of any art or trade but a training of the mind, a formation of habits of study, of insight and the easy handling of ideas" (Sir Clifford Allbutt) and of people. These qualities take hold readily and firmly in this the most formative and plastic year of professional life. Physicians are developed—especially when exposed to investigatively oriented teaching—who are self-propelling learners and questors of excellence throughout their professional careers and who can discern what is important from what is unimportant—no mean achievement of an education. No one expects to learn all the important facts in one subject and much less can one become even oriented in all the several aspects of clinical medicine covered by a rotating internship; information is important but it is remarkable, is it not, how quickly much of it becomes out-of-date! But one can acquire in a year of organized, focused experience under inspiring guidance in several aspects of one discipline, high standards, sharp critiques and the ability to accurately and intelligently appraise, relate and apply data in the humane practice of medicine—probably the most tender and sensitive area of human relationships; these verities are never out-of-date! Physicians so trained and conditioned are prepared to meet the exigencies of future responsibilities in much wider fields of medicine; I have noted this too many times to have any doubts of its essential validity, e.g., effective battalion surgeons in World War II and in Korea after "straight" pediatric training!

But many if not most physician-educators do not agree with me and even if they did, there are now difficulties and impediments in respect to personnel and facilities insuperable for consummation of the ideal. The only current plan for much of the graduate training in medicine is the partial solution inherent in the rotating internship—one, and less commonly, two years in duration. At its best, pediatrically speaking, this is minimal and wholly inadequate. The Academy, in my opinion, should assume leadership in bringing about reformation in this matter so far, certainly, as pediatrics is concerned in cooperation with the American Medical Association, the American Academy of General Practice, the Association of American Medical Colleges and any other groups willing to assist. (Action has begun in Canada, I am happy to report.)

Why?

In this country there are some 40 million potential and very important pediatric clients for physicians, namely, that number of persons under 15 years of age; in Canada there are some three million such clients. In the United States, according to the Academy Survey, 75% of these children under private medical care will receive it from the physicians in general practice who will spend 29% of their time in such work; only 11% of the patients were cared for by pediatricians.

How is the general practitioner trained at the graduate level to meet this responsibility? By such pediatrics as he gets for the most part in a one year rotating internship common in all states and required for licensure in 13, of which only 2 specify in any detail the required content of the internship. In one of these 2 states, the required amount of pediatrics was until recently 2 weeks; it is now 4! The Academy Survey states that "about half of the general practitioners had received less than one month of pediatric training during their hospital internship or had no pediatric service at all." Because of

this slim fare, the general practitioner-to-be not only fails to receive child health orientation as such, but he misses the valuable teaching of the concepts of comprehensive medicine which pediatrics is inherently best equipped of all clinical disciplines to render.

The Council on Medical Education and Hospitals of the A.M.A. does "not have available in any organized form, data regarding pediatric services in hospitals approved by the Council" (personal communication), but each of us knows many hospitals in which the one year rotating internship offers little or no pediatrics. The Academy of General Practice recommends "that physicians planning to enter general practice devote a second year to in-residency training in general surgery, medicine, obstetrics and pediatrics . . . and it is expected that family doctors will continue their education after they are in practice and will keep up with advances in all fields in which they practice" (personal communication). But can any "course" take the place of actual supervised clinical work with children!

The question being discussed is not whether the ideal is that all children be under the care of pediatricians or of general practitioners; the very practical point I am making is that—call him what you will—every physician who takes responsibility for child care should have supervised training in pediatrics.* I think we should set as a minimum goal six months of pediatrics in two year rotating internships. If there are to be officially recognized one year rotating internships, three months of the time should be devoted to pediatrics wherever facilities make this assignment possible. In accepting this as good, let us not be deceived into thinking it is best. There is no short cut to excellence; the fact is, as Dr. Gregg wisely says, that a good medical education takes not four years but eight or ten, whether it be for practice, for teaching or research." It seems to me that if we are not to lengthen the ideal graduate training of physicians, time must be salvaged by closer integration of college and professional school work, and both might become thereby more meaningful. Some time might be salvaged for pediatrics in rotating internships from that spent in teaching operative technics.

The next aspect of pediatric education to which I turn affects not only our specialty but all areas of medical teaching. I refer to psychology and to psychosomatic and sociologic medicine. These areas educationally overlap and integrate to a degree which makes discussion of them as a unit advisable.

Child psychiatry as it deals with psychopathologic disorders and their treatment does not lie essentially in the pediatric sphere. The greatest needs here are for more qualified personnel and for adequate study homes for the residential care of psychopathic patients; there is a great dearth of these facilities and they are desperately needed. But child psychiatry in its broad aspects has a large stake in the training of physicians in comprehensive or integrated pediatrics which is concerned with the health, growth and development as well as the sickness of the child, with the prevention, if possible, of behavior disorders as well as the prevention of infectious diseases and nutritional ailments. Here, the pediatrician, psychologist and psychiatrist must find an effective *modus operandi* for work together; I do not admit that there is not already a friendly desire to do so—indeed,

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* By "pediatrics" is meant here organized and supervised child care; it may be classified as preventive, medical or surgical pediatrics, and it may be located in newborn nursery, nursery school, emergency room, outpatient clinic, well-baby conference, convalescent home, parent or affiliated institution.

quite the reverse. In this general area of activity there are courses, study centers, research councils, rooming-in projects, and conferences of many varieties. And in the psychosocial or sociologic domain, preceptorships, family and home practice, general practice clinics.

The aim of the "course"—many of which are given in the preclinical years—is well-described by Dr. Alfred Washburn; it is, he says, of "Medicine as Human Biology" given by his group, "to stimulate the student to give thought to the nature of his life-long study —to help him to an awareness of what he needs to learn to become the wise and beloved physician—and to give him this beginning insight into the nature of his educational task as he starts his study of the sciences basic to medicine."

. . . The concept of the growth, the development and the endless adaptations to environment of a person from conception to death serves as a unifying and integrating appreciation of the responsibilities of the physician; it pulls together the basic sciences and clinical disciplines into a unitary field of knowledge which is Medicine."

Child psychiatrists and psychologists have made valuable and far-reaching contributions to knowledge of children's mental development and emotional behavior. What they have to offer pediatricians is summarized topically by the Committee on Child Psychiatry of the Group for the Advancement of Psychiatry. The areas of special contributions are those relating to:

1. personality growth and development;
2. interviewing technics;
3. child-parent-physician relationships;
4. psychologic reactions of children and parents to physical illness (acute and chronic) and to convalescence; and
5. psychopathology and symptom formation.

"Ideally," in the opinion of the committee, "in the education of emerging pediatricians, the content regarding the emotional life of the child, interpersonal relationships, etc. outlined above, should be taught by a well-trained pediatrician in collaboration with a child psychiatrist familiar with the pediatric setting and integrally a part of it. However, in most instances the programs cannot be carried out in this way and the instruction—both individual and staff—will probably become the task of the child psychiatrist." But not, I think, for an indefinite period. Each time a new skill or technic comes into medicine there is fractionating for a time and then integration; dealing with the emotional life of the child is not much more specialized at this moment than is pediatric cardiology for example. In at least a dozen clinics, comprehensively minded doctors—pediatricians and child psychiatrists—in collaboration with psychologists and social workers are laboring in all earnestness to work out ways—for surely there is more than one way—of orienting and training students and staff in this least well-charted area of child health—the psyche.

In order that the roles of home and family and socio-economic forces in medical practice may be recognized and implemented in the training of undergraduate and graduate students of medicine, several programs are being developed. The proponents of these projects seek also to reduce the fractionating of student-patient relationships—a deplorable but inevitable occurrence in the current practice of rotating students and interns through various clinical services, and even various sectors of a single service. In several clinics, home as well as hospital experience for students is operating in the form of home calls on newborns and sick patients; the assignment on a voluntary basis of preclinical students

to families as health visitors or advisors on a four year basis; on the establishment of general practice clinics. In some schools, there is a very active preceptorship program in operation—poor or good educational experience depending upon the caliber of participants. Certainly some improvement in the educational activities of teaching centers to give trainees at every level of experience greater continuity in doctor-patient contact is needed. One small facet in which there is progress is the participation of pediatricians in prenatal clinics making possible and natural subsequent contact with the family at least through the newborn period. In one medical school all pediatrics is concentrated in a three months period (in the fourth year) devoted almost exclusively to this one subject; some small measure of continuity in student-patient contact is thus made possible in simultaneous outpatient and inpatient experience. It is highly desirable that longitudinal student-patient contact as well as home-family care be extensively studied and developed.

Most of the programs dealing with psychologic growth and emotional development and those concerned with family and home practice are being carried forward in close association and collaboration with several departments, notably public health, preventive medicine, psychiatry and social service. I would like to offer a word of gentle caution and make a suggestion in regard to this development.

Out of the study and care of physically sick children grew interests and achievements in preventive pediatrics in its various aspects. It should never be forgotten that whatever else is important in clinical medicine the most fundamental of all our activities deals with adequate, accurate histories and with careful skillful physical examination coupled with a knowledge of pathology; we start from there no matter where we end! Nothing a physician can do so firmly establishes rapport between himself and his clients as careful histories and skillful physical examinations. That does not in any respect whatsoever imply that psychologic and sociologic factors are not truly and essentially vital aspects of sickness and health care. We do not debate what is more, what is less important, but simply emphasize what is always basic and comes first in the practice of a doctor of medicine! How to orient and teach in the less clearly defined areas and when to begin the special programs are *sub judice;* but they will come to fruition someday and in the meantime are subject to experimental study and appraisal. We must have open and receptive minds; there is no one and only approach; we must try many—understandingly, sympathetically, interestedly.

The suggestion I would make—not original—is that the skills, interest and advice of social scientists be utilized and that they be invited to join our pediatric teams. The investigators of social dynamics have much to offer in evaluating and appraising these programs now getting under way, especially since many sociologists are interested in studies of professional education in many fields. Did you ever consider, for example, the great psychologic and sociologic impacts of a medical center on a community! We here today are thinking in terms of pediatric education but that is a small segment of a vast array of influences, forces, conflicts, opportunities, facts which are engendering ferment in the lives of many people, extra- and intramural, in contact with medical centers. We are just beginning to envisage some of the far-flung implications of medical schools and hospitals to our society—the by-effects, one might say—of our immediate task of training competent physicians. From this point-of-view, what is really going on, psychologically and sociologically speaking, in medical Centers and what is really the over-all content of

medical education! Those are indeed questions to which adequate answers are greatly to be desired and earnestly sought in skillfully designed investigations.

The poet Robert Frost says,

> "We dance round in a ring and suppose,
> But the Secret sits in the middle and knows."

Concluding, may I make a trite but ever valid observation that the Secret lies less in curricula and programs and projects and more by far in the fine qualities of mind and heart of those students and teachers who see in medicine opportunities both for the advancement of scientific knowledge and for rendering comprehensive professional service to people respected as human beings who deserve physicians possessed of environing faith and private excellence!

SPECIAL ARTICLE

JOHN HOWLAND AWARD ADDRESS

By GROVER F. POWERS, M.D.
New Haven, Conn.

INTRODUCTION

Dr. Daniel C. Darrow, Hamden, Conn.: To me has fallen the pleasure and honor of presenting the second John Howland Medal to Grover Francis Powers. What I can say adds nothing to a life work which merits the highest recognition which American pediatricians can bestow on a colleague. Nevertheless those who have not had the opportunity to know and work with him would like to know something of the man.

He was reared and lived in Lafayette, Indiana, until he was graduated from Purdue. He received his medical degree at Johns Hopkins in 1913 and spent seven years at the Harriet Lane Home. During these years his friends and associates were the remarkable group of men who flocked to the first department of pediatrics in the United States which recognized that study of disease is the most important function. John Howland was assisted by Edwards A. Park, McKim Marriott, Kenneth Blackfan, James L. Gamble, Fred Tisdale, Graham Ross, Wilbur Davidson, Benjamin Kramer, Sam Clausen and others. What extraordinary careers stemmed from this outstanding opportunity to study diseases of children! Powers was influenced most by John Howland, McKim Marriott, Edwards Park, Kenneth Blackfan and Sam Clausen. Of his classmates George Washington Corner was closest. Of all this galaxy of stars, Grover Powers became the greatest as pediatrician—as master of the science and art of the care of sick infants and children. It is, therefore, enlightening to see what the relatively pure pediatrician can achieve as professor of pediatrics.

He brought to pediatrics a good mind which would have assured success in a number of fields. However, his spiritual qualities made the choice of pediatrics and teaching particularly fortunate. He is sensitive to a change in a situation to an almost unbelievable degree. This appears in his observations of patients, in his grasp of the essentials of experimental observations, and in his insight into world affairs. To most people Powers' sensitiveness is most obvious in his response to the sufferings of others and his suffering from misunderstandings arising from actions not guided by his own sensitiveness. Fundamentally he is a man in whom no ambitions for himself interfere with his judgment of a situation or a person. For a man so sensitive, his objectivity always astonished those who know him. He has the humility without which no one can rightly undertake to direct the lives of others. He once told me that he had prayed as a boy to have the courage to do what he thought was right. His prayer was answered for he always has the courage to do what he thinks right, but, as with all humble men, he has found it difficult to be sure that he is right. These qualities not only made him a great pediatrician but an ideal person to lead young men, for they always instinctively know that he understands their problems and that no selfish motives lie behind his decisions.

Throughout his life he has lived with sick infants and children as few internes do—watching and worrying over his patients. I have seen his equal in the diagnosis of disease and his superior in formal description of disease but not his equal in evaluating the effect of disease on a particular child nor the effect of therapy on the course of disease.

His substantial contributions to the study of disease appear as almost accidental incidents in the care of sick infants and children. In Baltimore he assisted in some of the work on rickets but it was the patients observed in New Haven that led to his best publications. He clarified the requirements for infant feeding by pointing out that infant food must contain sufficient calories, water, salts and other dietary essentials in mixtures giving certain proportions of the calories as protein, fat and carbohydrate. This simple straightforward analysis is so fundamental that the same rules can be used at all ages. Twenty-five years ago he instituted a program for the care of premature infants that is essentially the current one. At this time he also observed improvement in the nutrition of patients with celiac disease following injections of liver extract. From clinical observations he outlined a plan for treatment of infantile diarrhea that utilized all the lessons of the past and assigned a proper place to each procedure. He introduced the use of transfusions and correctly stated that shock, and not anemia, is the principal indication for transfusions. He was conscious of the deficiencies of this system but never deceived himself that more precise application of certain measures would improve the results. He always made me feel that someone must find out what had been omitted from his plan of treatment.

Dr. Marriott used to love to tell the following story that illustrates Powers' clinical astuteness. On finding Dr. Powers looking dejected, Marriott said, "Why so gloomy, Grover? We can now treat your babies with diarrhea." Powers replied, "That is just the trouble; seven infants died last night." Marriott said, "Come, now, you saw how much better they looked after we injected sodium bicarbonate." Powers replied, "Yes, I saw the improvement and you probably know what to do for acidosis, but do you know what to do for the babies? They used to live seven hours but they only last four now." Marriott always added that Grover was right and too much sodium bicarbonate had been given. All who have worked with Dr. Powers have received the benefit of this type of clinical judgment, since treatment and research cannot safely be isolated in the laboratory or precise clinical observations which neglect the experience and judgment of a good physician.

Trask and Powers formed a wonderful team for the study of infectious disease. I am sure Trask would agree with me that a great deal of Trask's work would have been impossible without Powers. The studies on the different reaction of infants, children and adults to streptococcal infections depended on the immunologist first trained in adult medicine and the pediatrician thoroughly familiar with these infections in children.

With the decrease in the mortality from infectious diseases, the apparent emergence of emotional disorders brought nothing new to the attention of Powers. He had early supported Drs. Putnam and Jackson. Eventually he would like to have placed the study of psychiatric disorders on the same basis as infections and metabolic diseases. He would have liked to have a pediatrician familiar with emotional disorders take care of somatic diseases and make detailed studies of appropriate cases demanding psychiatric study aided by men trained in special psychologic technics. He is keenly sensitive to emotional disturbances in infants and children but, from experience, he is afraid of any type of

medical care which separates sick children from doctors who understand the reactions to somatic disorders from firsthand observation.

Powers' greatest achievement has been the training of students to become physicians and house officers to become pediatricians. This has been accomplished largely by example. The pediatric department was organized so as to create a situation in which people learn about disease as well as treat disease. Powers feels that students and interns cannot be prepared to meet the future progress by merely observing the best of current practice. For the student to learn, the faculty must also be learning from the literature, from study of patients and by methods of research which practitioners cannot have time to master. Powers did not regard the presentation of the description of disease in lectures as an important function of a professor. Rather he strove to enlist the student and interns in his own activities of studying patients and problems presented by disease. The actual learning was the most important ingredient in the development of the physician and this had to be done by the student himself. Powers, as a fellow student with years of experience, could merely provide guidance and example and show the direction which their efforts should take. He regards the proper supervision of the work of the students and interns on ward rounds as the most important function and educational opportunity of the professor. His rounds were regarded as a trust. His relationship was that of a consultant—first on the needs of the patient and second on the opportunities for medical education. His attention seemed almost exclusively centered on the problem in hand. He was unhurried; and administrative functions and display of his own knowledge were forgotten in trying to come to the crucial problem presented by the sick child. As can be attested by many of this audience, the paths leading to wisdom in the care of sick infants and children have been revealed to those who caught the spirit of the ward rounds of Grover F. Powers.

Dr. Powers, in behalf of the American Pediatric Society I give you the second John Howland Medal. In concluding I quote from Thoreau—"I hear no good news, save certain traits of some noble character."

Mr. President, Dr. Darrow and Friends: This Award—christened in memory of my first pediatric chief, bestowed at its premiere last year upon my second (Dr. Park), and now presented to me on your behalf by a beloved, loyal and overgenerous colleague—is accepted with humble gratitude. I thank you not only for myself but also in behalf of my devoted wife and of many former associates in Baltimore, Detroit and Connecticut without whose support and encouragement over the years I would not stand here this afternoon.

I invite your attention to a brief consideration of "The Retarded Child and his Family as a Challenge to Pediatric Practice, Research and Education." I offer no apology for my subject. Here are major problems perhaps as old as human life itself but still too low on the totem poles of medical respectability and of scientific concern. We have recognized the problems but too many of us have done as the priest and Levite in the ancient parable

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—we have "passed by on the other side." The public is now alerted by press, radio, television, stage and personal solicitation to muscular dystrophy, cerebral palsy, poliomyelitis, heart disease, tuberculosis, "crippled children," cancer, multiple sclerosis, hemophilia, nephrosis. But consider! There are between one and two million retarded children in our country—we cannot know the exact number because there are no inflexible definitions and standards and no census. This is also an estimate, by the way, of the number of homes with, as it were, this special "skeleton in the closet"; too many families now so regard their problem! Assuming two parents and two siblings for the family unit of each retarded child, there are thus between 5 and 10 million persons blighted to a great or small degree by the direct impact on their lives of these unfortunate children. And then one must add to family sorrow, vast contingent sociological, economic, educational and legal disturbances, responsibilities and dislocations. The retarded child is found in the families of rich and poor alike; offspring of highly intellectual parents and of those of medium and low intelligence; the misfortune respects race, color and sex not-at-all; mental and physical capacities, as with normal children, range over a wide scale; social and emotional adaptability are not narrowly confined; and unwitting potentialities for and actualities of antisocial behavior and for public liability are tremendous.

Without in the slightest degree minimizing the validity of claims upon our sociologic, economic, medical and humanitarian interests and concerns in the other important areas mentioned—upon our purses, also, and on our heartstrings—can they individually (perhaps collectively) equal in sheer numbers the problems presented to society by mental inadequacy! Only the problem of mental illness are commensurate in size with those of mental retardation in respect to total population. It seems to me, therefore, that the major importance to biologic and social science, to medicine, to economics, to public policy, of retarded children is all too obvious.

When I was on Dr. Howland's house staff, I am sure the largest portion of his consultation practice lay in the field of mental retardation rather than, as one might expect, in the areas of his special interests, nutrition and metabolism. I imagine this situation exists today for most professors of pediatrics—certainly it was true of my own private work. I suppose the proportion is less for the general practitioner, but somewhat more relatively for the pediatrician than for the family doctor. The children are usually referred sooner or later to specialists of one kind or another and what, one may inquire, is accomplished by the usual medical round of examinations? By and large, relatively little save for a diagnosis and prognosis (or confirmation of those already made); these are too often incorrect from lack of knowledge or inadequate because made without the important data which continuing observation alone can furnish. When there is no cure, we doctors sometimes capitulate too easily to therapeutic defeatism forgetting that the physician is just as responsible for alleviating as for curing; action is just less urgent, not less vital. The shock, physical and emotional, when a diagnosis of mental inadequacy is made, is devastating to families and, to a lesser but very real degree, to the humanitarian physician. Because he is so often untrained in the skills requisite for working through the problems with the family and unaware of such community resources as exist (admitting that these are grossly underdeveloped), the physician is often brusque and, in effect, seems to reject because of his own inadequacies the total situation leaving the family in pitiful loneliness with crushing feelings of guilt and disgrace to often uppermost in their minds. Is it any wonder that in families of retarded children there occur divorces, suicides and

mental illness attributable to unresolved problems associated with their unfortunate child!

Should not the physician, rather, act on the precept that a doctor is a doctor at all times and in all situations where there is suffering and not find interest and resource solely where cure is probable! Should he not develop skills and technics here as in other areas of medical practice whereby he may help parents in their hour of black despair and offer them requisite time and encouragement to talk over implications and potentialities and possibilities and also give them insight into community resources which he has perchance helped to develop! The inadequacies of physicians account for much of the medical "shopping around" in which families of retarded children indulge, spending money which often could be more beneficially used for care and training.

Derivation of the world "idiot" suggests that it originally denoted a peculiar or private person—one "set apart," so to speak. And so the retarded child was regarded for centuries—shunned, neglected, forgotten, often the butt of the practical joker and sometimes the unwitting prey of malicious or unscrupulous persons who used him for purposes of money-making in sideshows or in criminal acts. Only under rare circumstances did groups go to the other extreme and regard certain persons of feeble intelligence and peculiar personality as possessed of magic or superhuman powers and worthy of worshipful attention. A gradual change has come in the attitude of society since Itard and Seguin (only 150 years ago) demonstrated that retarded children were trainable and in many cases could become useful participants in the stream of life instead of persons "set apart" on the shore. There are many other great names associated with the problems of mental retardation—but not really "many" considering the magnitude of the subject, its long recognition and in comparison with the more numerous students of many other and less extensive and urgent problems.

Over the years, progress has been made chiefly in the development and elaboration of the ideas and concepts of Itard and Seguin on the importance of training and conditioning of these children to a measure of self-help and often of service to the community. This process extends even to those of very low intelligence. The important rôle of training and conditioning is emphasized by the ever-increasing stress upon them as our major remediable resource. Institutions are being oriented away from purely custodial functions to those of rehabilitation. I am sure that many of the artisans of the past and present are intellectually inadequate judged by scholastic standards, but it is amazing what imagination and skilled craftsmanship and ingenuity are exhibited under the right environment of stimuli, skills and encouragement. It is difficult for me to believe that the amazing feats of idiot savants do not represent a development which could be used to advantage at least as a subject of modern psychologic research. The Southbury Training School opened in 1940; in 12 years there have been 2,327 admissions and approximately 342 children (15%) have been sent out on job placements; the earnings of these children to date is $1,327,813.00. In addition, 200 children (9%) have been returned to their homes, to foster homes or to community facilities where they are getting along acceptably even though some are of very limited ability. In the domain of extramural activities, of course, one is always faced with the problem of over-protection and failure to appreciate the encouragement which comes with self-accomplishment.

Parents themselves have come to the rescue of the professional workers and are helping their children and themselves mightily thereby. I refer to organization of parent groups in small communities, in cities, nationally and as parent-teacher associations in institutions

for retarded children both privately and state operated. There are an increasing number of small institutions operated by groups of parents for their own children—a development which should be actively encouraged.

Another accomplishment of parent groups in which they are "way out in front" is in creating local diagnostic and guidance centers where parents may learn of suitable day-care nurseries, boarding homes, institutions for continuous care, special schools and special classes, recreational and occupational facilities and job placement services for the larger number kept in their homes. In these centers the skilled teacher, the social worker, the psychologist are vital members of teams with the physician offering counseling over a broad area.

One aspect of the usefulness of group meetings of perhaps prime importance is their psychotherapeutic value to parents themselves. Here they learn the extensiveness of the problem; the possibilities for hopeful prognosis; the fact that the misfortune affects families irrespective of economic, social or intellectual attainment; the fact that they are not alone in their sorrow and that what is faced by one most likely is being faced and resolved, perchance, by others. Parents often cease to whisper, so to speak, and conceal; the "skeleton in the closet" to which I referred earlier is brought out and examined and is found to have many relatives and companions. False ideas of guilt and disgrace are often in some measure mitigated or dispelled. In place of these destructive thoughts and imaginings come constructive ideas and plans. Programs and projects are developed which are focused on the enrichment of community resources and the improvement of schools, institutions, clinics and other facilities. The rôle of these parent groups in "raising the sights" of officials and professional personnel of private and public schools and of institutions for care of retarded children and in maintaining high standards and high morale is of incalcuable importance.

The local and national parents' organizations have concerned themselves principally with pressing forward in the fields of training and education; the National Association for Retarded Children (organized only three years ago) has committees on Education and on Research (among others) which anticipate strong public support. Local parent groups last year raised a million dollars for their own projects—a fact which shows how much strength now lies in these primary regional organizations; no doubt the National Association will achieve with maturity enthusiastic acceptance and support.

This parent movement is a "grass roots" project in the truest sense, developing as it did from the small local units to a national association; it is fraught with potentialities for great good if sound leadership is followed. It is the parents' own effort to supplement and augment the contributions of professional and governmental groups in meeting the manifold problems their children present—a "crusade" in driving power and initiative and one in which trained personnel and friends are happy to cooperate—but not as members for this is largely a parents' affair, a characteristic which is probably unique, or was on its inception.

Turning now to the research challenge of the problems associated with intellectual inadequacy one can assert that in the last few years there has been an awakening of parents, educators, physicians, scientists of various disciplines and of enlightened public officials to the many aspects of this subject which are open to and ripe for scientific inquiry.

Leo Kanner has recently stated: "At long last, the study of intellectual inadequacy is

regaining its rightful place as an important sector of medicine. One hears less and less about the rather supercilious notion that the subject of feeblemindedness has been exhausted and offers no reward to the investigator. The walls of traditional indifference which have surrounded 'institutions' are crumbling fast. The discovery has been made, belatedly but definitely, that systematic research promises to enrich not only the knowledge of mental deficiency as such but also the total scope of human ecology and human engineering."

Many others see the situation as does Dr. Kanner as evidenced by the establishment of research centers and the convening of seminars and symposia on this and allied subjects and under a variety of auspices. With problems so protean in nature and so vast in scope, a multi-disciplined approach is absolutely essential. In this area, as I see it, there exist rich possibilities for the geneticist, the experimental embryologist, the biochemist (especially those studying what Garrod called "inborn errors of metabolism"); for investigators of prenatal, natal and postnatal insults and traumata (including assaults from radiation, blood anomalies and infections); for the endocrinologist who is extending his relevant inquiries beyond the cretin; for students of congenital defects, their experimental production and correlation with intellectual handicaps; and for the psychologist and psychiatrist who, aided by the newer technics, may find in the controlled environment of a training school and in subjects lacking the intellectual subtleties of the average person, special incentives for the study, interpretation and treatment of behavior and emotional disorders. Other promising areas are those of seizures, of experimental neurosurgery and of electroencephalography. Studies of causation of mental defectiveness criss-cross the entire field of congenital malformations. Facts which are applicable in the one area are of importance in the other as well as to convulsive disorders, cerebral palsy, congenital heart disease, skeletal defects and other structural deficiencies.

I am making no attempt, obviously, to exhaust possibilities but simply to remind you of those areas which at this moment, as you well know, are at the front of the research firing line. In every field I have suggested there have been recent developments of first-rate scientific importance: and who can deny that from them there may come in good time knowledge of causes which may lead to preventive or alleviative measures which might be applicable to sectors, even if only small ones, of this multifaceted field of inquiry!

I have been emphasizing fundamental research dealing largely with such matters as causation, prevention and pathology; of necessity, most of such research must be carried on by teams of scientists in institutions of one kind or another under controlled conditions. But one should recall here that the larger number of retarded children (perhaps 80 or 90%) are living in their own or in foster homes. Here, also, research is urgently needed, research in the areas of pedagogy and social science and social service; the student of education will find in this field special incentives for the development of new ideas on methods and procedures of, perhaps, general applicability; and there are rich opportunities for exploration in sociology and social service.

The query is simply phrased: "How can retarded children be successfully cared for in homes?"—but the problems and the answers are difficult and complex and needful of much study and exploration. What is required and beneficial for the child itself? for siblings? for parents? What facilities and programs are indicated for day nursery care, for kindergardens, for special classes, for recreation, for occupation? What degree of supervision and counseling is desirable and by whom? Visiting nurse? teacher? medical

social worker? psychiatric social worker? psychologist? How may psychologic and psychiatric counseling and guidance be advantageously utilized for the whole family unit? What are the ways and means of obtaining and developing the wide variety of needed community services and resources?

These and kindred types of investigations in the fields of pedagogy, public health, social sciences and social service present themselves both to workers and to families caring for retarded children and are proper subjects for research.

But from whence comes the inquiring mind, the questing spirit, the technical know-how! Obviously from many groups, but I shall speak only regarding those of which I have personal experience—the young men and women in the laboratories and clinics of our medical schools.

For about 12 years in the Department of Pediatrics at Yale and in the Southbury Training School, I have had the opportunity of observing in an integrated educational program, residential in part, what to me is an ideal situation for teaching by example and by doing students, interns, residents, fellows and nurses in this field; their interests, for a time at least, are channeled in the multifaceted aspects of the problems of the intellectually handicapped child including the psychologic and educational as well as the medical. This program was designed primarily to enrich the educational experience of the professional participants—as should be the aim, in my opinion, of all decentralized teaching. But if widely practiced, the impact of many such programs would bear dividends of incalculable scientific and educational values to institutions and to those they serve; the secondary results might thus well rank in importance with primary purpose and accomplishment.

I realize fully that there are at least three primary requirements for the successful operation of a program such as that developed in Connecticut. These are:

1. Reasonable geographic propinquity.

2. Enlightened administrative leadership at both the institutional and trustee levels; the training school concerned may be a private institution as effectively as one managed by the state.

3. At the training schools there must be teaching by word and by example of a high degree of professional scholarship and practice; in order that such competence exist, there must be ever present the spirit of inquiry and curiosity, the faith that new truths may still be found in this ancient but ever new dominion of human endeavor. The clinical resources are present in all institutions and often, also, laboratories, libraries and technical equipment—but above all else there must be inspired, informed professional leadership in medicine, psychology, education and, I may rightfully add, social science and institutional management.

In any of these fields (except the last named) it is difficult for me to conceive of the requisite high quality of professional leadership being furnished by anyone who at the same time bears the heavy responsibilities of institutional administration—a major undertaking in and of itself which requires special training in management. The directors of medical and psychologic services and of education and training should be free to devote their whole time and interests to service, teaching and investigation in their respective fields. Under this kind of organization, one may expect to develop trained personnel and to produce scholarly contributions.

What are some of the values which may accrue from a liaison and partnership of this type? I shall list some of them.

1. Teaching of students, undergraduate and graduate, centered on concentrated and varied neurologic material including congenital malformations; experience would be got specifically in the problems of mental retardation—diagnosis, natural history, care and training of children, psychologic and social evaluation—and in making effective and kindly contacts with and interpretations to families. These institutions are source material also for studies in preclinical as well as clinical disciplines, in genetics, in public health. Is it not heartening to consider the contributions which even the mentally handicapped may thus make and are making to science!

2. Contacts of medical participants with other aspects of an integrated approach to a special problem—general medicine, psychology, psychiatry, radiology, dentistry, education, social service, public health—knowledge and experience which are useful in general pediatric practice.

3. Experience and often participation by junior personnel in scientific investigations which may or may not have foreseeable practical applicabilities.

4. There are many problems of a general medical nature presented in the population of an institution for retarded children. Clinical experience and research are thus available and indicated over a broad area. As examples, studies in poliomyelitis, infectious hepatitis, bacillary dysentery, Rh incompatibility, infectious lymphocytosis, streptococcosis and fluoridation of water have been carried out at the Southbury Training School. Varied medical experience is offered which affords a sort of rotating internship but having the vital requisite ordinarily lacking—integrated medical direction and guidance. There is also available in the cottages, home practice, as it were, dealing with ordinary medical conditions in contrast to the exotic ones seen predominately in many hospital services these days.

5. Affiliation of training schools with university departments of medicine, psychology, psychiatry, social science and education enhances the prestige and morale of training school personnel—something which should not be needed but definitely is at this time. One need but recall here the rise in professional standards in hospitals following the introduction of clinical clerkships into programs of medical education. As parents are becoming more willing to bring skeletons out of closets, so may we anticipate that the professional activities of training schools will not for long be regarded as sinecures for those with second rate abilities but rather as challenging opportunities for those of superior intellectual gifts.

6. Money must be spent and facilities provided in institutions for mentally retarded children to supply medical care; under enlightened leadership this money and these facilities could at the same time do double duty and provide educational opportunities in wide areas of scholarly endeavor, provided of course that competent personnel are available to quide and direct.

7. Programs such as these depend for success upon the existence of the very situation they hope to create—an adequate reservoir of gifted and inspired professional personnel. We look with confidence to the day when there will be a comfortable balance between supply and requirements.

In conclusion, may I comment that these remarks are based on the professional experience of one who has dealt with the matters discussed on a clinical and humanitarian basis. But I have faith that science will discover causes and will furnish knowledge upon which better methods of prevention, care and treatment will be developed; contraception,

sterilization and eugenic mating may well fill expanding rôles as forms of biological purging. Euthanasia we shall never accept regardless of degree of mental inadequacy so long as civilization means reverence for all human life—not just certain lives.

In the meantime, I find words of Sir Thomas Browne beautifully expressive of a working, sustaining and humanitarian philosophy:

"Since the stars of heaven do differ in glory; since it hath pleased the Almighty hand to honour the north pole with lights above the south; since there are some stars so bright that they can hardly be looked on, some so dim that they can scarce be seen, and vast numbers not to be seen at all, even by artificial eyes; read thou the earth in heaven, and things below from above. Look contentedly upon the scattered difference of things, and expect not equality in lustre, dignity, or perfection, in regions or persons below; where numerous numbers must be content to stand like lacteous or nebulous stars, little taken notice of, or dim in their generations. All which may be contentedly allowable in the affairs and ends of this world, and in the suspension unto what will be in the world to come; when the last may be the first, and the first the last; and when Lazarus may sit above Caesar; and the just, obscure on earth, shall shine like the sun in heaven; when personations shall cease, and histrionism of happiness be over; when reality shall rule, and all shall be as they shall be forever."

NEWS AND ANNOUNCEMENTS

Seventh International Pediatric Congress

The Seventh International Pediatric Congress will be held at Havana, Cuba, Oct. 12 through 20. The Congress will include: 6 plenary sessions; 14 round tables; free subject sessions; a scientific exhibit; presentations by European and North and South American authorities, and an entertainment program.

For reservations and further details, write the Organizing Committee of International Pediatric Congress, Hospital Mercedes, Vedado, Havana, or write Gomez Tours, Havana.

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Postgraduate course in pediatric allergy at the New York Medical College, Flower and Fifth Avenue Hospitals, New York City, Nov. 4, 1953, through May 31, 1954. This course consists of lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds, and animal experimentations. For further information: Dean, New York Medical College, 106th Street and Fifth Avenue, New York City.

* * *

Dr. Leona Baumgartner, Assistant Commissioner of the Department of Health in charge of maternal and child health services, has resigned to become Executive Director of the New York Foundation. The New York Foundation was organized in 1909 and has been mainly interested in the fields of education, social welfare, medicine and public health. As its name implies the New York Foundation has largely limited its activities to New York City.

Dr. Harold Jacobziner, now director of the Department's Bureau of Child Health, has been named Assistant Commissioner to succeed Dr. Baumgartner.

* * *

The Gesell Institute of New Haven, Conn., has no relationship to Yale University. It is a private institution and Dr. Gesell and his associates have no connection whatever with the Yale Child Study Center. The Yale Clinic of Child Development, popularly known as the "Gesell Clinic," was brought to an end when Dr. Gesell retired from Yale in 1948.

* * *

The following diplomates have been certified by the American Board of Pediatrics, Inc.:
Ann Arbor, Mich.—June 26, 27 and 28, 1953

Adler, Norman Nathaniel, U. S. Army Hosp., Fort Eustis, Va.
Ainsworth, Louise Powers, 350 E. Broad St., Columbus, Ohio
Anderson, Ray Carl, 2841 41st Ave. South, Minneapolis
Berg, George Shepard, 1st Lt., 2108-1 ASU, USAH, Camp Breckenridge, Ky.
Berg, John William, 313 Fifth St., Ames, Iowa
Bergstrom, William Hugo, Dept. of Ped., Syracuse Mem. Hosp., Syracuse, N.Y.
Boersma, Vernon L., 97 E. 30th St., Holland, Mich.
Borges, Wayne Howard, 927 Brunswick Rd., Cleveland Heights, Ohio
Brodsky, Emanuel David, 3805 Kingsley Court, Harrisburg, Pa.
Brown, Harold Zelig, 6230 Wilshire Blvd., Los Angeles
Calodney, Martin H., 7407 Buckingham, Clayton, Mo.
Costello, Paul Joseph, 1138 Elm St., Manchester, N.H.
Dawson, Katherine E., 4592 N. High St., Columbus, Ohio
Edelman, Samuel A., 14 Soundview Ave., White Plains, N.Y.

Elghammer, W. Robert, 1113 Grant St., Danville, Ill.
Eubank, David Furman, 3744 N. Whipple, Chicago
Feinauer, Lyman R., 2598 E. 2760 South, Salt Lake City
Fijan, Kenneth J., The Lincoln Clinic, 1036 Stuart Bldg., Lincoln, Neb.
Fong, Willis M., 4723 6th St. N.E., Seattle
Forer, Robert, 434 Bellevue Ave., Trenton, N.J.
Forney, John L., 1930 Truxtun Ave., Bakersfield, Calif.
Frank, Max, Box X, Talmage, Calif.
Frank, Minnie, 1933 S. Harding St., Chicago
Gillick, Edward E., Jr., 457 Third St., Niagara Falls, N.Y.
Gilmore, Robert L., 4833 W. Peterson Ave., Chicago
Gormley, C. James, 4 Cushman St., Plymouth, Mass.
Harris, Leon A., 416 N. Bedford Drive, Beverly Hills, Calif.
Hauser, Donald Charles, 2873 Holmes Ave., South, Minneapolis
Hudson, Phoebe, 1744 N. Wood St., Wilmington, Ohio
Kagay, Charles L., 406 Harries Bldg., Dayton, Ohio
Kalinowski, Aloysius A., 131 Linwood Ave., Buffalo, N.Y.
Katz, Benjamin E., 519 Main Avenue, West, Twin Falls, Idaho
Kinsell, Clift Seybert, 15 E. Arrellaga St., Santa Barbara, Calif.
Kolle, Fred Wynne, 105 Hawes, Wharton, Texas
Krevsky, David A., 2015 Fort St., Lincoln Park, Mich.
Ledis, Seymour, 1st Lt., 2796th Med. Gp., Norton AFB, San Bernardino, Calif.
Lendrum, Bessie Lieberman, 1368 N. Sedgwick St., Chicago
Lerch, Theodore Trowbridge, 725 Fourth St., Marysville, Calif.
Lewis, Philip Lewis, 180 Adams, Denver
Liebling, Wilbert, 5830 Overhill Dr., Los Angeles
Lienke, Roger Irving, Dept. of Ped., State Univ. of Iowa, Iowa City
Lissauer, Charlotte B., 473 W. End Ave., New York City
Lo Presti, Joseph Michael, Children's Hospital, 13th and W Streets, N.W., Washington, D.C.
Luce, Ralph R., 607 38th Ave., Seattle
Lynn, James Wiley, Jr., Dept. of Ped., Strong Mem. Hospital, Rochester, N.Y.
McMahon, William J., 503 Third St., Niagara Falls, N.Y.
MacKinney, Loren Greenwood, Children's Hospital, 219 Bryant St., Buffalo, N.Y.
Matthews, Norman L., Northern Michigan Children's Clinic, Marquette, Mich.
Mouton, Charles M., 3942 Denker Ave., Los Angeles
Muller, Richard P., 308-C Hesse Ave., Apt. 940, Daly-Lewis Acres, Scott AFB, Ill.
Newton, Joseph R., Building 542, Apt. 2, Fort Monmouth, N.J.
Orme, Harry William, 3103 Lomina, Long Beach, Calif.
Pearce, Earl Barrie, 1202 Broadway, Longview, Wash.
Peck, Charles Eugene, III, 21801 Lake Shore Blvd., Euclid, Ohio
Plummer, Lois J., 131 Linwood Ave., Buffalo, N.Y.
Post, David B., Lovelace Clinic, 4800 Gibson Blvd., S.E., Albuquerque, N.M.
Rathkey, Arthur Stanley, 1st Lt., Hill AFB, Base Hospital, Ogden, Utah
Reedy, Mary Ellen, 105 S. York St., Elmhurst, Ill.
Reichert, John M., 1791 Howard St., Chicago
Robin, Sidney W., 4753 N. Broadway, Suite 614, Chicago
Roth, Arthur, 5387 Miles Ave., Oakland, Calif.
Sacks, Martin Oscar, 10459 S. Artesian St., Chicago
Sapin, Samuel O., 453 E. 14th St., New York City
Schiff, Lester H., 1202 Niagara St., Niagara Falls, N.Y.
Seagle, Joseph Bowman, 2 Patricia Court, Champaign, Ill.
Shepard, Kenneth Sihler, 2703 Sheridan, Evanston, Ill.
Shibuya, Madoka, Babies' Hospital, Broadway and 167th St., New York City
Shick, Paul Ellsworth, Jr., 3919 S.W. Cullen, Portland, Ore.
Siebers, Bernard Herman, 1945 Lafayette Ave., S.E., Grand Rapids, Mich.
Swift, Frank Louis, U. S. Army Hosp., Fort Belvoir, Va.

Takenaka, Kameichi, 704 21st Ave., Honolulu
Trivette, Parks Dewitt, 12 Second Ave., N.E., Hickory, N.C.
Veasy, Lloyd George, Dept. of Ped., College of Med., Univ. of Utah, Salt Lake City
Waldman, A. Martin, 2940 Jerusalem Ave., Wantagh, L.I., N.Y.
Washington, Edward L., 909 University Ave., Columbia, Mo.
Waterman, Donald Frederick, 1425 Burke Ave., N.E., Grand Rapids, Mich.
Weil, William B., Jr., 2065 Adelbert Rd., Cleveland
Wetzel, Dick Davis, Madigan Army Hosp., Tacoma, Wash.
Whitworth, Rex Hancock, 104 San Miguel, Salinas, Calif.
Wilborn, Sam Werner, 609 W. 15th St., Austin, Texas
Wingert, Willis A., 545 W. 12th St., Claremont, Calif.
Zenger, Doris Baker, Pantigo Lane, East Hampton, N.Y.

The Board announces the following oral examinations: Miami—Oct. 9, 10 and 11, 1953, and Indianapolis—Dec. 4, 5 and 6, 1953.

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Dr. Joseph A. Baird, Pittsburgh, died May 2, 1953. He was a Fellow of the Academy.

* * *

Dr. Luther W. Holloway, Jacksonville, Fla., died May 8, 1953. He was a Fellow of the Academy.

BOOK REVIEWS

COLLEGIATE EDUCATION FOR NURSING, Margaret Bridgeman, New York, Russell Sage Foundation, 1953, $2.50.

The continuous and increasing need for more nurses and better prepared nurses has stimulated self appraisal in the field of nursing education. Guidance for future planning is essential in order to meet the health needs of society.

This report is a critical investigation of existing educational facilities by Dr. Margaret Bridgeman, former academic dean of Skidmore College.

The author analyzes the deficiencies in supply and the probable future demands, both quantitative and qualitative.

Her recommendations for development of nursing curricula based on educationally sound principles and integrated in the general educational system should effectively guide educators, nurse educators and all who are interested in providing health services in their future planning.

TRAUMA, GROWTH AND PERSONALITY, Phyllis Greenacre, New York City, W. W. Norton & Company, 1952, $4.50.

Dr. Phyllis Greenacre is a distinguished psychoanalyst on the staff of Cordell University Medical College, where for many years she has been influential in the teaching of psychiatry and the interpretation of behavior to students in medicine. This volume is a collection of papers which the author has read and published in the past decade. The pediatrician needs to be very sophisticated in matters of medical psychology in order to benefit from reading any of these essays on such topics as weeping and urination, predisposition to anxiety, and infantile aggression. However, since the author frequently goes back into infant behavior for material, those pediatricians with training in medical psychology and child development, and/or psychoanalysis, will find here many provocative ideas which should help interpret some of their own clinical experiences with infants and children. Dr. Greenacre is herself a clinician and for that reason illustrates theoretic concepts freely with clinical anecdotes. If attempts are made to read this book, plenty of time must be left for perusal and cogitation.

CHILDREN IN PLAY THERAPY, Clark E. Moustakas, McGraw-Hill Book Company, Inc., 1953, $4.50, 218 pp.

One of the lacks in the training of the pediatrician is that of experience with healthy children. In some training centers, attempts are being made to overcome this deficiency by providing nursery schools where pediatricians may observe children in play and in interaction with other human beings. Physicians, teachers and parents alike are not aware enough of the use of play and its role in providing opportunities for learning, and for expressing feelings. This book attempts to help parents and professional people in a better understanding of children through this medium of self expression. Written by a psychologist on the staff of the renowned Merrill-Palmer School, the uses of play by healthy children are described as providing outlets of tension and frustration, as well as of joy and sensuous pleasure. The play of emotionally disturbed children is also illustrated. Verbatim tape recordings of children in play provide the evidence. The author, who has also worked as a psychotherapist, describes in detail how he has interviewed parents and structured play situations which were beneficial to the child and meaningful to the parents and therapist.

This reviewer was left with a feeling of uneasiness after reading the book because the author did not point out enough the dangers which lie in any so-called "therapeutic situation" which is guided by persons inexperienced and untrained in psychotherapy. As the author points out, play can be loaded with emotion and feeling, and in the hands of the amateur therapist play situations can have the explosive potentials of dynamite. It is to be hoped also that parents reading this book will not become so subjective in their interpretation of their children's play that anxiety is fostered in all persons concerned. Play for children outside the child guidance clinic needs to continue to be spontaneous; if analyzed too minutely in terms of motives and psychologic implications, there may result some of the very problems we are attempting to prevent.

In Memoriam

JOSEPH STILES WALL, M.D.
1876-1952

THE imprint which an individual leaves on the minds and in the hearts of his colleagues and friends is engraved by many qualities: honesty, integrity and humility in religion, science, teaching and service. He possessed these in great measure—Dr. Joseph Stiles Wall, whose death occurred on September 18, 1952. He left a heritage of accomplishments deeded to the American Academy of Pediatrics, his associates in Washington and his numerous friends and patients.

Dr. Wall lived a religion of self sacrifice in his devotion to his profession and his colleagues. He spent many of his most productive years in his local medical society affairs, serving on various committees, and was elevated to the Presidency in 1926. During this immediate period he had devoted himself and his time to the passage of the law to regulate the Practice of the Healing Arts in the District of Columbia, a law which became a model for the entire country. For this and other "outstanding services to the medical profession of Washington" and "his contributions in the field of Pediatrics, and his unselfish devotion to the health needs of the children of the District of Columbia," Dr. Wall was honored on two occasions by the District of Columbia Medical Society: November 26, 1929, and September 28, 1948.

His pediatric colleagues in the District of Columbia and the Staff of Children's Hospital, recognizing his unselfish services, expressed their appreciation on two occasions: a testimonial dinner on his election to the Presidency of the American Academy of Pediatrics; and a dinner on the completion of 50 years of service to Children's Hospital. The Board of Directors of Children's Hospital has designated the Auditorium of the Hospital as the "Joseph Stiles Wall Auditorium" in recognition of his efforts in the erection of the new building and his long service to the hospital.

As a teacher Dr. Wall was an artist. His diction was perfect, his knowledge of related sciences was unlimited. He delighted in quoting the Bible, Shakespeare, or the Greek philosophers in pointing up a problem. His students listened and respected. He brought to present day scientific discussion a rare ability to analyze the new technics in clear clinical interpretation and treatment. He had taught chemistry and physiology at Georgetown University Medical School after his graduation in 1897. His interest in the welfare of children sent him later to New York and Oxford for further training. On his return to Washington, he became one of the few physicians who limited their practice to the diseases of children. He later became Professor of Pediatrics at the Georgetown University Medical School and for the outstanding contributions to the University he was given the degrees of Master of Arts in 1925 and Doctor of Science in 1938.

Dr. Wall became interested in the American Academy of Pediatrics early in its history. The Academy recognized his outstanding ability in the field of legislation and he was Chairman of the Committee for many years. It would be impossible to evaluate his service to the Academy, and the medical profession generally. To him "social medicine" was as

the setting sun to medical freedom. He fought "socialized medicine" in no unmistakable terms. The encroachment of Government in medicine, and pediatrics in particular, found a worthy opponent. He was never dismayed by the might of social interests, nor faltered in aggressive attacks on their activities. He took every opportunity to appear before Congressional committees to fight this trend. At the same time he acclaimed the need for improved programs for the welfare children, both as a member of the Advisory Board to the Children's Bureau and an active proponent of the Study of Child Health Services of the Academy. It is well to refer to page 171 of "A History of the American Academy of Pediatrics" to read the citation to Dr. Wall in February 1947, by the Academy.

Not only did Dr. Wall serve the Academy of Pediatrics with utmost devotion in the area of the United States, but he was intensely interested in the problems of the Latin American region. President Gram Martin of Cuba recognized this friendship and bestowed upon him the Decoration of Merit, Order of Carlos L. Finlay, in 1947.

The public honors accorded Dr. Wall stemmed from his innate interest and respect for the individual; this fundamental quality was his greatest attribute. He listened with attention and sympathy, he responded with wisdom and kindness. He was considerate and understanding of his subordinates. He could understand inexperience and immature judgment but could not tolerate inefficiency or lack of initiative. His judgment was fair and honest and his integrity unquestioned. These qualities made up the character of the man.

Dr. Wall added his bit to the "mosaic of things."